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OPIUM ADDICTION

VI. THE EFFECTS OF ABRUPT WITHDRAWAL FOLLOWED BY READMINISTRATION OF MORPHINE IN HUMAN ADDICTS, WITH SPECIAL REFERENCE TO THE COMPOSITION OF THE BLOOD, THE CIRCULATION AND THE METABOLISM *

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Continuing our studies on a series of male opium addicts, we wish to report the results obtained when the morphine administered to supply the patients' needs was abruptly withdrawn. These results include studies made at three hour intervals for a twenty-four hour period following the last administration of morphine and another series of results obtained when the drug had been stopped for forty-eight hours. Following the studies at the close of the forty-eight hour period, morphine was again administered to allay all suffering and again the same observations and studies were made.

EXPERIMENTAL PROCEDURE

Two separate methods of approach were used in the study of changes brought about by the abrupt withdrawal of morphine which was being administered to supply the addict's need. One group was studied at intervals of three hours following the last administration of the drug; in four cases the studies were carried over a period of twenty-four hours. Another group of ten patients was studied immediately following the administration of the regular scheduled dosage, and the studies were then discontinued except for observations on the behavior until the end of a forty-eight hour withdrawal period, when the same studies were again made just before and after morphine was given again to allay all symptoms.

Only four of the eight patients selected in the first group were studied over periods of three hour intervals for twenty-four hours.

* Submitted for publication, March 5, 1929.
* From the Narcotic Wards of the Philadelphia General Hospital.
* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City, and were carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

The behavior and cooperation of the others were not conducive to accurate observations. No food was given during this period. The addicts were always required to remain in bed for a period of one-half hour before any studies were made.

Figures showing the pulse and respiration rates are the average of a five minute count. The figures for the blood pressure were obtained from as many patients as it was possible to measure the blood pressure of accurately within a five minute period, followed by a record of temperatures taken both by mouth and by rectum. When these observations were finished the basal metabolic rate was determined with Krogh's apparatus for recording basal metabolism, following which a sample of blood was drawn from a vein at the elbow. At the end of each period, the subject passed a sample of urine.

The procedure in the study of the group in which the drug was abruptly withdrawn for a period of forty-eight hours was quite similar. Following the administration of the last regular scheduled amount of morphine in the morning, the subjects immediately reclined in bed without breakfast and observations were made on circulation and respiration, and a sample of blood was taken after a rest period of half an hour. The subjects then resumed the standing position for a period of five minutes, and observations were made. A sample of blood was taken for analysis, and following this the addicts were subjected to the staircase climbing test which we have described in detail in another paper.[1] Except for observations concerning their conduct and remarks, further studies were not made until the completion of the withdrawal period. Food was allowed during the first thirty-six hours of this period, but in no cases was any taken at the expiration of the first twenty-four hours. At the end of the withdrawal period the addicts were again requested to recline, and the same observations were conducted: blood was drawn and the staircase climbing tests were again carried out.

With the completion of these observations and studies, the addicts were given sufficient morphine to supply their needs. As soon as they professed to feel normal the same studies, including the drawing of the blood and the staircase climbing tests, were again carried out.

RESULTS

In table 1 we have tabulated the highest, lowest and average figures of the determinations and observations, together with the number of cases studied at three hour intervals for a period of twenty-four hours following the abrupt withdrawal of morphine. The word "basal" in the table indicates the results obtained immediately following the last injection.

1. Light, A. B., and Torrance, E. G.: Opium Addiction: III. The Circulation and Respiration of Human Addicts During the Administration of Morphine, Arch. Int. Med. **43**:556 (April) 1929.

TABLE 1.—*Studies of Human Opium Addicts at Three Hour Intervals for a Period of Twenty-Four Hours Following the Withdrawal of Morphine*

		Basal	3d Hour	6th Hour	9th Hour	12th Hour	15th Hour	18th Hour	21st Hour	24th Hour
Pulse	No. cases	8	8	8	5	5	5	4	4	4
	Highest	80	76	78	76	74	73	75	78	80
	Lowest	58	57	53	51	55	63	60	57	67
	Average	68	62	64	68	64	66	69	70	74
Blood pressure while reclining	No. cases	8	8	8	5	5	5	4	4	4
	Highest	125/84	119/79	120/84	130/78	130/85	135/82	118/71	112/69	118/72
	Lowest	103/65	105/60	103/61	107/60	104/61	108/63	104/59	101/58	106/66
	Average	116/74	114/70	114/71	116/69	112/70	118/71	110/67	107/65	112/69
Respirations	No. cases	8	8	8	5	5	5	4	4	4
	Highest	18	15	15	23	22	18	16	16	15
	Lowest	11	11	10	12	11	12	9	9	10
	Average	14	13	13	17	15	15	13	12	13
Temperature by mouth	No. cases	8	8	8	5	5	5	4	4	4
	Highest	98.8	98.7	98.7	99.0	99.1	99.4	99.0	99.6	101.1
	Lowest	97.3	97.6	97.2	98.1	98.4	98.5	98.6	98.8	99.2
	Average	98.4	98.4	98.2	98.5	98.6	98.9	98.8	99.0	99.7
Rectal temperature	No. cases	8	8	8	5	5	5	4	4	4
	Highest	99.6	99.4	99.7	99.6	99.7	99.8	99.9	100.6	101.9
	Lowest	98.0	98.7	98.0	98.7	98.9	98.8	99.4	99.6	99.9
	Average	99.2	99.1	99.2	99.2	99.4	99.3	99.6	100.0	100.7
Hemoglobin	No. cases	8	8	6	3	4	4	4	4	4
	Highest	19.8	19.1	20.3	15.9	16.1	16.5	18.6	18.2	17.9
	Lowest	14.1	10.8	13.2	9.3	12.9	11.2	15.6	12.6	16.2
	Average	15.8	15.5	16.2	12.3	14.6	14.6	17.2	15.9	17.3
Erythrocytes	No. cases	8	8	7	5	3	5	4	4	4
	Highest	4,940	5,000	5,680	4,865	4,740	4,870	5,010	5,360	5,050
	Lowest	3,850	3,910	3,850	3,910	4,530	4,600	4,280	4,240	4,100
	Average	4,527	4,506	4,517	4,521	4,490	4,718	4,547	4,747	4,515
Leukocytes	No. cases	8	8	7	5	3	5	4	4	4
	Highest	15,400	14,600	15,600	9,400	8,800	11,200	11,400	11,500	12,900
	Lowest	4,000	5,600	7,800	7,300	7,000	7,200	10,400	10,400	9,000
	Average	8,980	9,888	10,771	8,020	7,800	9,700	10,925	10,825	11,125
Polymorphonuclears	No. cases	8	8	8	4	3	5	4	4	4
	Highest	77	79	74	66	59	69	73	76	77
	Lowest	48	48	51	46	53	55	67	65	72
	Average	61	61	61	58	57	63	69	70	75
Lymphocytes	No. cases	8	8	8	4	3	5	4	4	4
	Highest	46	44	43	42	41	39	27	30	24
	Lowest	19	18	19	28	34	24	23	19	18
	Average	33	33	33	34	36	30	25	24	20
Large mononuclears	No. cases	8	8	8	4	3	5	4	4	4
	Highest	6	6	8	9	6	6	5	7	5
	Lowest	2	3	1	5	3	3	4	3	4
	Average	4½	4	4½	6	4	5	5	5	4½
Eosinophils	No. cases	8	8	8	4	3	5	4	4	4
	Highest	3	5	4	6	3	2	2	2	1
	Lowest	0	0	0	0	2	1	0	0	0
	Average	1	2	1	2	2	1	1	1	½
Basophils	No. cases	8	0	8	0	3	0	0	0	0
	Highest	2	0	1	0	2	0	0	0	0
	Lowest	1	0	0	0	0	0	0	0	0
	Average	½	0	½	0	1	0	0	0	0
Urea	No. cases	4	4	4	2	2	2	4	4	4
	Highest	12	13	13	10	10	10	15	13	17
	Lowest	8	8	9	10	9	8	10	10	9
	Average	10	10	11	10	9.5	9	11.5	11	11.5
Sugar	No. cases	8	8	8	4	4	4	4	4	4
	Highest	107	111	113	107	93	100	107	111	109
	Lowest	60	83	78	63	69	76	80	89	100
	Average	86	94	91	84	81	86	91	100	105
Creatinine	No. cases	4	4	4	2	2	2	4	4	4
	Highest	1.25	1.31	1.2	1.12	1.08	1.2	1.55	1.58	1.5
	Lowest	1.085	1.145	1.11	1.05	1.07	1.18	1.03	1.07	1.08
	Average	1.145	1.24	1.17	1.08	1.075	1.19	1.28	1.32	1.28

TABLE 1.—*Studies of Human Opium Addicts at Three Hour Intervals for a Period of Twenty-Four Hours Following the Withdrawal of Morphine—Continued*

		Basal	3d Hour	6th Hour	9th Hour	12th Hour	15th Hour	18th Hour	21st Hour	24th Hour
Calcium	No. cases	4	4	4	2	2	2	4	3	4
	Highest	10.46	10.97	10.82	10.50	10.8	10.4	10.48	10.38	11.63
	Lowest	9.84	9.23	9.12	9.03	9.45	9.63	9.99	6.53	9.90
	Average	10.15	10.22	9.99	9.76	10.12	10.01	10.19	8.47	10.72
Magnesium	No. cases	2	2	....	....	....	....	3	3	3
	Highest	2.12	2.08	....	....	....	....	1.84	1.98	1.80
	Lowest	2.06	2.0	....	....	....	....	1.64	1.46	1.50
	Average	2.09	2.04	....	....	....	....	1.75	1.64	1.61
Specific gravity—plasma	No. cases	8	6	8	4	3	4	4	3	4
	Highest	1.0282	1.0277	1.0296	1.0287	1.0281	1.0284	1.0283	1.0287	1.02931
	Lowest	1.0238	1.0238	1.0238	1.0239	1.0243	1.0239	1.0247	1.0249	1.02576
	Average	1.0261	1.0256	1.0263	1.0263	1.0257	1.0264	1.0261	1.0262	1.02687
Protein, per cent	No. cases	8	7	8	4	3	4	4	4	4
	Highest	8.32	9	9.28	8.66	8.31	8.66	8.25	8.60	8.77
	Lowest	6.91	6	6.57	6.51	6.62	6.57	7.09	7.03	7.03
	Average	7.81	7.65	7.86	7.85	7.58	7.88	7.65	7.80	7.94
Conductivity	No. cases	8	7	8	4	3	4	4	4	4
	Highest	143	148	139.2	139	137.6	137.2	147.0	144.4	147.0
	Lowest	130	133	133.6	136	133.0	135.0	142.6	138.4	140.2
	Average	136.1	137.6	135.4	137.2	135.4	136.0	144.1	142.4	143.3
Basal metabolism	No. cases	6	6	6	4	3	3	4	4	4
	Highest	20	14	19	11	6	24	14	14	36
	Lowest	—6	—12	2	6	—1	8	—9	—9	12
	Average	6	2	8	8	2	14	5	5	22

There was a slight average rise in the pulse rate and a slight fall in the systolic pressure. The average red blood cell count remained practically the same with a slight increase in the hemoglobin. A slight average increase in the white cells appeared, with a relative increase of polymorphonuclear cells and a decrease in the lymphocytes. Physical and chemical studies of the blood did not reveal any significant changes except for a slight fall in two cases in which the amount of magnesium present was determined and a slight rise in the conductivity of the serum found. A slight rise in the temperatures both by mouth and by rectum was noted. The average figure for basal metabolism shows a definite increase from +6 to +22. The cooperation of the patients, however, at the end of the twenty-four hour period was obviously not as good as when determinations were made following the last administration of the drug. Chemical and microscopic examination of the urine in the cases in which the drug was abruptly withdrawn failed to reveal the appearance of albumin or casts as well as any other positive signs. It was noted that the color of the blood drawn from the same vein without stasis in the same persons at three hour intervals varied considerably. If the addict complained of feeling hot, the blood flowing into the collecting tube was bright red, suggesting a high percentage saturation of oxygen. On the other hand, if the addict complained of feeling chilly at the time, the blood was much darker in color, leading one to the belief that there existed a low percentage saturation of oxygen.

The physical changes noted in the addicts as the studies were carried on varied considerably. In the four cases in which the proposed twenty-four hour period of withdrawal was carried to completion the patients gave the observers the impression that they were suffering with a common cold in the head, lacrimation, sneezing and difficulty in breathing through the nostrils. Yawning was also present in these four cases, although it was not frequent. Dilatation of the pupils began between the sixth and ninth hour interval, in all cases. The patients complained of chills and exhibited the characteristic pilomotor activity of the skin known as "cold turkey" at the end of eighteen hours. Four showed slight muscular twitchings at the end of sixteen hours. None of the patients vomited, although at the end of the twenty-four hour period two complained of a serious gnawing sensation in the stomach which they interpreted as the need for the drug. Three addicts had a bowel movement at the end of the eighteen hour period without the aid of medication, something unusual with them while taking drugs at regular intervals. At the end of the twenty-four hours, two of the addicts showed a decided change in disposition, becoming extremely surly and repeatedly stating that they hoped we would stop our "foolishness" and give them their drug. At the end of eighteen hours, one patient was seized with a spell of laughter sufficient to produce severe lacrimation. He expresed his condition as a "laughing yen."

The results obtained during comparative studies following the last administration, at the end of the forty-eight hour withdrawal period and following the readministration of the drug, are tabulated in table 2, and the results of the staircase climbing tests in table 3. Chart 1 shows graphically a comparison of the results of the staircase climbing tests obtained during the three different phases of study.

The most significant positive observations in these studies were a definite increase in the number of white cells with a relative increase in the polymorphonuclear cells and a decrease in the lymphocytes at the end of the withdrawal period. Following the readministration of the drug, there was still a slightly further average increase in the number of white cells. Two cases, however, failed to show any increase in the number of white cells. On the other hand, one of our cases showed an increase in the number of white cells of from 8,100 to 27,000 at the end of the forty-eight hour period and reached 31,000 one hour after the readministration of the drug when all the withdrawal symptoms had apparently disappeared. A count taken six hours later showed a still further increase to 34,000. Twenty-four hours after the readministration of the drug, they had fallen to 14,000. This addict required 10 grains (0.65 Gm.) of morphine a day, the same amount required by one of our patients whose leukocytes numbered 8,300 at the beginning of the withdrawal period and who had the insignificant rise to

TABLE 2.—*Studies of the Effect on Human Opium Addicts of the Abrupt Withdrawal of Morphine for a Period of Forty-Eight Hours and Its Readministration*

		Before Abrupt Withdrawal	At End of 48 Hour Abrupt Withdrawal	After Readministration of Morphine at End of 48 Hour Withdrawal Period
Pulse rate while reclining	No. cases	10	10	10
	Highest	80	71	83
	Lowest	52	50	54
	Average	64	61	69
Pulse rate while standing	No. cases	10	9	9
	Highest	112	112	123
	Lowest	59	73	88
	Average	79	93	107
Blood pressure while reclining	No. cases	10	10	10
	Highest	138/92	140/84	129/79
	Lowest	102/60	109/63	88/60
	Average	120/73	121/73	111/71
Blood pressure while standing	No. cases	10	9	9
	Highest	130/90	138/94	112/90
	Lowest	86/64	110/74	80/60
	Average	110/79	116/85	98/77
Respiration	No. cases	10	8	8
	Highest	22	24	34
	Lowest	12	11	12
	Average	17	16	17
Hemoglobin	No. cases	10	10	7
	Highest	16.7	18.9	18.1
	Lowest	13.2	14.8	13.8
	Average	15.1	16.9	15.6
Erythrocytes	No. cases	3	2	2
	Highest	4,827	5,150	5,550
	Lowest	4,450	4,300	4,500
	Average	4,609	4,700	5,025
Leukocytes	No. cases	9	9	8
	Highest	13,100	27,800	34,000
	Lowest	7,500	7,800	8,000
	Average	9,800	15,200	16,980
Polymorphonuclears	No. cases	7	9	7
	Highest	78	97	86
	Lowest	47	52	56
	Average	62	72	68
Lymphocytes	No. cases	7	9	7
	Highest	46	40	39
	Lowest	20	2	12
	Average	33	25	27
Large mononuclears	No. cases	7	9	7
	Highest	7	6	4
	Lowest	0	0	0
	Average	3	1	2
Eosinophils	No. cases	7	9	7
	Highest	2	2	3
	Lowest	0	0	0
	Average	1	1	2
Basophils	No. cases	7	9	7
	Highest	1	1	1
	Lowest	0	0	0
	Average	1	1	1
Urea	No. cases	3	4	5
	Highest	15	16	18
	Lowest	11	10	11
	Average	13	13	15
Sugar	No. cases	3	4	5
	Highest	101	115	126
	Lowest	69	85	93
	Average	93	101	107
Cholesterol, whole blood	No. cases	10	7	8
	Highest	215	235	250
	Lowest	163	175	150
	Average	189	208	189

TABLE 2.—*Studies of the Effect on Human Opium Addicts of the Abrupt Withdrawal of Morphine for a Period of Forty-Eight Hours and Its Readministration—Continued*

		Before Abrupt Withdrawal	At End of 48 Hour Abrupt Withdrawal	After Readministration of Morphine at End of 48 Hour Withdrawal Period
p_H blood	No. cases	3	4	4
	Highest	7.51	7.51	7.45
	Lowest	7.37	7.43	7.38
	Average	7.45	7.46	7.42
Dry matter, whole blood	No. cases	10	10	7
	Highest	22.7	24.5	23.3
	Lowest	20.1	21.7	16.2
	Average	20.7	22.6	21.9
Dry matter, cells	No. cases	6	9	8
	Highest	40.8	43.6	55.3
	Lowest	38.2	37.5	27.4
	Average	41.3	40.7	41.2
Dry matter, plasma	No. cases	10	10	8
	Highest	10.2	11.5	11.4
	Lowest	8.2	9.2	8.4
	Average	9.1	10.1	9.9
Schneider's score	No. cases	8	7	7
	Highest	15	12	11
	Lowest	1	9	1
	Average	10.4	10	4
Oxygen percentage saturation of venous blood	No. cases	..	6	6
	Highest	..	60.7	79.1
	Lowest	..	39.3	49.2
	Average	..	42.5	62.2
Red cells, per cent by volume	No. cases	6	10	7
	Highest	38.7	43	45.0
	Lowest	34	37.3	35.0
	Average	36.2	40.2	39.1

8,500 at the end of the period. The two addicts who did not show a change in the number of leukocytes appeared to suffer as much as the other eight who showed definite increases.

The red blood cells were studied in only two cases and showed a slight rise after the abrupt withdrawal and a further slight increase following readministration of the drug in both cases. Determinations of hemoglobin by means of the Newcomer plate in ten cases showed an average rise of from 15.1 to 16.9 Gm., and in eight of these it remained practically the same after the readministration of the drug. The rise in hemoglobin occurred in all our cases as did the slight increase in the red cell volume following abrupt withdrawal.

The results obtained from the determination of the dry matter in the whole blood and plasma showed an average increased concentration of the blood of about 9 per cent. This tendency for a concentration was true in all the cases studied and following readministration of the drug did not return to the figure obtained before withdrawal. The dry matter of the cells remained unchanged.

Further studies showed no significant changes in the urea nitrogen, sugar and p_H of the blood. A slight rise of the cholesterol of the whole

blood was noted at the end of the abrupt withdrawal and a return to the same average figure following the readministration of the drug as that obtained before the withdrawal was begun. This rise of cholesterol was present in five of the seven cases studied.

In six cases studies of the percentage saturation of the venous blood drawn from the same vein at the elbow, following the abrupt withdrawal of the drug compared to the results obtained following the readministration of the drug, show an average increase in the percentage satura-

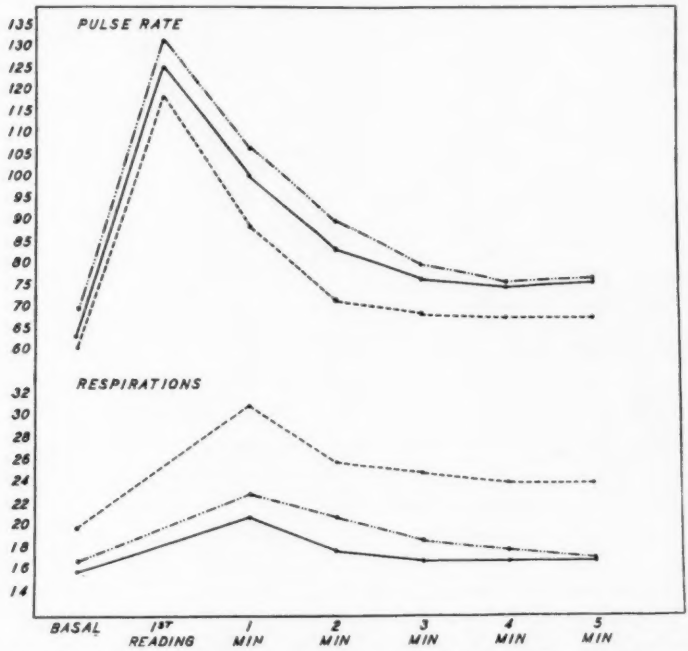

Chart 1.—Average changes in pulse and respiration rates in response to the staircase climbing test in a group of human addicts receiving morphine, after withdrawal of morphine for forty-eight hours and following readministration of morphine after the forty-eight hour withdrawal period. In this chart and in chart 2, the solid line indicates, during administration; the broken line, after forty-eight hours, and the dash and dot line, following readministration.

tion of from 42.5 to 62.2 per cent. This rise in percentage saturation of the oxygen in the venous blood was present in all our cases.

The circulatory changes noted during these studies consisted in a slight fall of the average pulse rate while the patient was reclining during the abrupt withdrawal and a slight rise in the average rate following the readministration of the drug. A study of the individual

cases, however, shows this fall to be present in only six of the ten, the other four showing slight rises during the withdrawal period. The average rise of the pulse rate while the patient was reclining following the readministration of the drug occurred in nine of the ten cases, the other showing a slight fall in the rate.

The average pulse rate, determined while the patient was standing, increased fourteen beats per minute at the end of the forty-eight hour period, with a further average increase of fourteen beats following the readministration of the drug. In all individual cases, the patients showed this increase of pulse rate while standing following withdrawal

TABLE 3.—*A Comparison of the Average Increase in the Pulse Rate, Respiration and Systolic Pressure and the Changes in Diastolic Pressure Following the Staircase Climbing Test on Human Opium Addicts Before Withdrawal, After a Forty-Eight Hour Period of Withdrawal of the Drug and Following the Readministration of Morphine*

	1st Reading	1st Minute	2d Minute	3d Minute	4th Minute	5th Minute
Pulse (9 cases)						
Before withdrawal	62	37	20	13	11	12
At end of withdrawal	58	27	11	8	7	7
Following readministration of drug	62	37	20	10	16	7
Respiration (9 cases)						
Before withdrawal	..	5	2	1	1	1
At end of withdrawal	..	11	6	5	4	4
Following readministration of drug	..	6	4	2	1	0
Systolic pressure (9 cases)						
Before withdrawal	29	30	25	16	9	4
At end of withdrawal	23	21	12	9	6	2
Following readministration of drug	18	19	15	13	8	4
Diastolic pressure (9 cases)						
Before withdrawal	−10	−7	−6	−6	−6	−6
At end of withdrawal	−6	−4	−2	−3	−0	−2
Following readministration of drug	−8	−1	2	4	3	7

compared to the figure obtained at the beginning of this period as well as the further increase following the readministration of the drug.

No change was present in the average systolic pressure, taken while the patient was reclining, at the beginning of the withdrawal period as compared to that at the end of the period. Individual cases, however, showed some marked changes. In one case, the systolic pressure rose 37 mm. In another it fell 20 mm. The others showed rises and falls ranging from 2 to 7 mm. of mercury. An average rise of 6 mm. in the systolic pressure was noted when the figures for the average systolic pressure determined while the subject was standing, following the withdrawal period as compared with those obtained at the beginning of this period. An analysis of the individual cases shows that four of the ten exhibited this rise; in two the pressure remained the same and in three it showed a slight fall. An average fall in the systolic pressure taken while the patient was standing was noted in the ten cases following

the readministration of the drug compared to the average systolic pressure, taken while the patient was reclining, at the beginning and end of this period. Seven of the ten cases showed this fall; in one the pressure remained the same and in the other two it showed slight rises. The greatest fall encountered was 23 mm.

Following the readministration of the drug, the systolic pressure taken while the subject was standing showed an average fall of 18 mm. compared to the average obtained at the end of forty-eight hours and 12 mm. compared to the average pressure at the beginning of the withdrawal period. Following the readministration of the drug, all cases without exception showed this fall in the systolic pressure while the patient was standing.

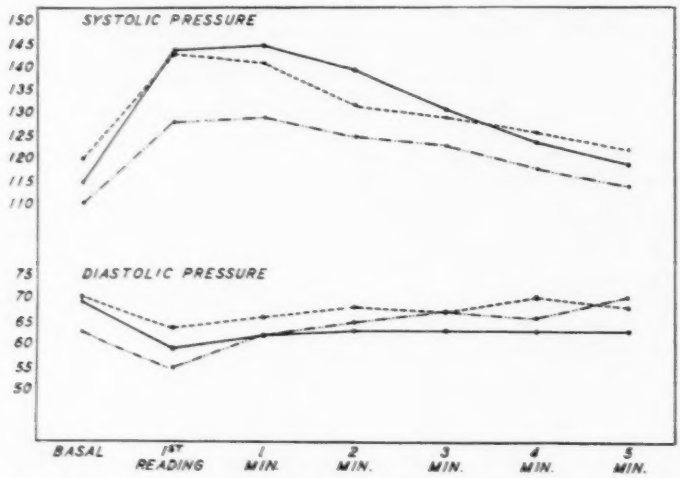

Chart 2.—Average changes in systolic and diastolic blood pressure in response to the staircase climbing test in a group of human addicts receiving morphine, after withdrawal of morphine for forty-eight hours and following readministration of morphine after the forty-eight hour withdrawal period.

Schneider's test of physical fitness,[2] conducted in eight cases at the beginning of the withdrawal period, gave an average score of 10 points, the same as the average at the end of the forty-eight hour withdrawal period in seven cases. Following the readministration of the drug, the average score of the seven cases fell 6 points. This fall was directly due to the increase in the individual pulse rates and fall in the pressure when the subject changed from the reclining to the standing postures.

2. Schneider, E. C.: A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1507 (May 29) 1920.

Studies of the staircase climbing test at the beginning and end of the forty-eight hour period and following the readministration of the drug do not reveal any great changes in the response of the circulatory system to this rather fatiguing test. If anything, the response following the end of the forty-eight hour period when the addict complained of extreme muscular weakness was more similar to that of athletes than when the drug was being administered at regular intervals. The immediate increase in the respiratory rate at the close of the withdrawal period following the climbing of the staircase was the only indication of a poorer response to this test when compared to the test at the beginning of the period and following the readministration of the drug. The response following the readministration of the drug as measured by the reaction of a trained person was poorer than when the addict was suffering, except the respiratory increase. We found that trained normal persons met the stress of climbing with the greatest rise in pressure and the least rise in pulse rate, and showed the quickest return to normal.[1]

No changes were noted in the respiratory rates while the patient was reclining either at the end of the forty-eight hours or following the readministration of the drug as compared to the figures obtained at the beginning of withdrawal. Individual cases also showed only small and insignificant changes, with the exception of one case in which the respirations were 17 at the beginning of withdrawal, 20 at the end of the withdrawal period and 34 following the readministration of the drug.

Only two of our cases showed a slight rise in temperature during this period. The highest temperature reached was 100.2 F.

Chemical and microscopic examination of the urine showed the presence of a trace of albumin in two cases, but neither one showed the presence of any casts. All other examinations of the urine gave negative results.

Attempts to determine the basal metabolism of the gastro-intestinal tract, gastric analysis, ingestion of barium for roentgenograms and dextrose for dextrose tolerance tests were futile, the cooperation of the patient being so poor as to cause us to abandon the attempts.

The general behavior and symptomatology of these addicts were uniform during the forty-eight hour withdrawal period. All cases showed the characteristic pilomotor activity and the lacrimation, sneezing and excessive yawning. Five of the ten patients vomited, and all had normal bowel movements at the end of twenty-four hours. Three developed diarrhea at the close of the forty-eight hour period. In four cases, sweating was marked, beginning at the end of thirty-six hours. Muscular twitching, particularly of the muscles of the face and extremities, was present in all cases. One of our patients had a violent twitch-

ing of the muscles of the left leg which he himself attempted to stop by improvising a tourniquet by means of a towel. At the close of the forty-eight hour period, one addict complained of diplopia, and on examination he had a definite weakness of the right external rectus muscle. The average weight lost by the ten addicts was 5¾ pounds (2.6 Kg.), the individual losses ranging from 4 to 8½ pounds (1.8 to 3.8 Kg.). The addicts presented a picture of dehydration; the features were drawn. The face, neck and upper anterior part of the chest had a peculiar color which we can describe best as a "dirty flush."

Not one of the addicts wished to continue the experiment following the twenty-four hour period, and the begging and pleading for morphine for the following twenty-four hour period became extremely trying. Our judgment in selecting these addicts to act as subjects was based on their willingness to cooperate when requested to do so while the drug was being administered. This judgment proved to be poor, for those who offered the least resistance in persuasion turned out to be the most annoying at the end of the first twenty-four hours of the withdrawal period. One patient refused absolutely to continue at the end of thirty-six hours unless given a ¼ grain (16 mg.) of morphine to help him through the remaining twelve hours. He was given a hypodermic injection of sterile water and promptly went to sleep for a period of eight hours, with a tourniquet which he had improvised from a towel on his left leg to prevent muscular twitchings. He was awakened by the pain resulting from too tight application of the tourniquet. This addict never became aware of the fact that he was given nothing but sterile water. We wish to state, however, that such dramatic results with hypodermic injections of sterile water are rare; in most instances the addict cannot be fooled with this substitution, particularly following treatment.

While the studies were being conducted, changes for the better in disposition and disappearance of abjection could easily be noted at the end of the forty-eight hour withdrawal period just prior to the readministration of the drug. The anticipation of the morphine that was soon to be had seemed to have a distinctly beneficial action. A few minutes after the administration of the drug, all the addicts complained of a heavy feeling in the stomach; usually they also smiled and said that they were now experiencing the heavy sensation in the stomach that would bring relief. Despite the fact that within half an hour the addicts said that they felt normal and stronger than ever, the muscular twitchings about the face were still present in some cases. The patient who developed diplopia during the withdrawal period claimed to be entirely normal within forty minutes except that he was seeing double. Tests of the ocular movements revealed the presence of a weakness of the right external rectus muscle for several hours following the readministration of the drug.

We found the cessation of lacrimation, sneezing, yawning, pilomotor activity, muscular twitchings, the return of normal color to the face and the changes in disposition most striking following the readministration of the morphine.

COMMENT AND LITERATURE

Our observations covering the abrupt withdrawal periods resulted in a failure to find any symptoms or signs that have as yet not been described in the literature.[3] Our studies of the circulation, respiration and blood contribute nothing new, except for the discovery of a tendency toward a concentration of the blood and a slight rise in cholesterol during the abrupt withdrawal period. Morat [4] thoroughly described the appearance of leukocytosis at some time during the period of rapid withdrawal in a series of twenty-eight cases. Morat found this leukocytosis present in all his cases, whereas only eight of our ten cases showed it during the period of abrupt withdrawal. Studies of the blood of addicted dogs during withdrawal of the drug led Valenti [5] to the conclusion that vasoconstrictor substances were present in such blood, but this observation could not be confirmed by Pellini and Greenfield.[6] These authors were unable to detect any chemical changes in the blood of addicted dogs during the withdrawal stage. Plant and Pierce [7] found no change in the blood calcium of a dog who displayed violent symptoms during withdrawal of the drug.

We believe that our most important contribution to the study of withdrawal symptoms is the many negative observations obtained in these studies. This failure to find any marked changes, with the exceptions already mentioned, at the end of the withdrawal period as well as following the readministration of the drug, is open to criticism as we did not carry the experiments far enough. Our experience with these

3. Communication from G. H. Smith, Esq., to Dr. Johnson: On Opium Smoking Among the Chinese, Lancet **1**:707, 1841-1842. Levinstein, E.: Die Morphiumsucht, trans. by Charles Harrer, 1878. Sollier, P.: La demorphinisation et le traitement rationel de la morphinomanie, Semaine méd., 1894, p. 146. Bishop, E. S.: Narcotic Addiction, a Systemic Disease Condition, J. A. M. A. **60**:431 (Feb. 8) 1913.

4. Morat, D.: Le sang et les sécrétions au cours de la morphinomanie et de la désintoxication, Thèse de Paris, 1911.

5. Valenti, A.: Experimentelle Untersuchungen über den chronischen Morphinismus; Kreislaufstörungen hervorgerufen durch das Serum morphinisticher Tiere in der Abstinenzperiode, Arch. f. exper. Path. u. Pharmakol. **75**:437, 1914.

6. Pellini, E. J., and Greenfield, A. D.: Narcotic Drug Addiction: II. The Presence of Toxic Substance in the Blood Serum in Morphin Habituation, Arch. Int. Med. **33**:547 (May 15) 1924.

7. Plant, O. H., and Pierce, I. H.: Studies in Chronic Morphine Poisoning in Dogs: I. General Symptoms and Behavior During Addiction and Withdrawal, J. Pharmacol. & Exper. Therap. **33**:329 (July) 1928.

men at the end of a forty-eight hour period convinces us that such studies could be carried out only in institutions in which other methods than simple persuasion might be used.

The incessant begging and the annoying behavior of the addict during the withdrawal period becomes at times almost unbearable and may well react on the casual observer, so warping his judgment as to lead to conclusions that would not have been reached except for the behavior of the addict. Any one dealing with this group of people is fully aware of the pernicious influence they exert. It has been our frequent experience to leave the wards with the firm conviction that these men are not organically sick, the whole picture being an emotional one, and that the viciousness attached to the picture could best be coped with in penal institutions. Just as frequently we have entered the ward and found these men suffering with violent muscular twitches, vomiting, perspiration and yawning and showing such a sickly appearance that we have been convinced that there must be an organic basis for their apparent suffering.

In favor of an emotional basis as a cause for the withdrawal symptoms, we wish to cite our negative observations. Despite the fact that the addicts claim to be so weak as to be scarcely able to move, their response to the staircase climbing test was carried out with the same efficiency as when drugs were administered, with the exception of the respiratory response; following the readministration of the drug, the response was, if anything, poorer. Such differences as exist in basal blood pressure, heart rate and respiratory rate are too small to indicate any significant change. Addicts will admit that when they are unable to obtain drugs and when withdrawal symptoms with extreme weakness have become severe, the assurance of an available supply at a considerable distance will cause them to travel this distance with remarkable speed and efficiency.

The concentration of the blood and loss of weight would indicate some organic disturbance, on the surface, but we believe that these two positive manifestations can be explained on the basis that the addicts will not take food or water and perspire to such an extent that they cannot help showing this loss of weight and the degree of concentration of blood found in our cases.

Yawning, restlessness, vomiting, diarrhea, perspiration and extreme weakness are found in many emotional states. This type of behavior has frequently been observed by one of us in a group of football players as well as in the coaching staff of a university football team just prior to the playing of a so-called "important game." Loss of appetite, marked restlessness, frequent yawning, diarrhea and, occasionally, vomiting constitute the picture. The players will state that they are so

weak that they can scarcely move; yet, when the whistle starting the game is blown, all fatigue quickly disappears.

Further evidence that the picture of withdrawal symptoms has as its basis an emotional state is the response on the part of one of our addicts at the end of a thirty-six hour withdrawal period to the hypodermic injection of sterile water. Despite his obvious suffering, he immediately went to sleep and slept for eight hours. Addicts frequently speak about the "needle habit," in which the single prick of the needle brings about relief. It is not uncommon for one addict to give another a hypodermic injection of sterile water and the recipient to derive a "kick" and become quiet. On the other hand, it has been our experience just as frequently to have the addict know that he was given a hypodermic injection of sterile water and to have him fail to respond to its effect. Paradoxic as it may seem, we believe that the greater the craving of the addict and the severity of the withdrawal symptoms the better are the chances of substituting a hypodermic injection of sterile water to obtain temporary relief.

The presence of diplopia, marked increase in the number of leukocytes and albuminuria constitute sufficient evidence for one to look on withdrawal symptoms as having a true organic basis. Leukocytosis has been described in emotional states, but the degree reached in some of our cases, in four the leukocyte count being over 20,000 and in one reaching 27,000, would make one proceed with caution in the diagnosis of a clinical case before attributing such a count to pure emotionalism. Recently, however, Garrey [8] and his co-workers were able to establish a mental condition which frequently brings about an increase of from 100 to 300 per cent in the number of leukocytes. It is the belief of these observers that they are dealing merely with a redistribution due to fluctuation in the capillary bed in which leukocytes are trapped in the nonfunctioning capillaries.

White cell counts on the football players already cited made daily for a week before an important game and just prior to the game when they were showing symptoms of yawning, diarrhea and restlessness and complaining of extreme weakness failed to show any change from the normal count.

Muscular twitches are, at times, of such magnitude as to preclude any possibility of pure nervousness. The presence of albumin in the urine, mentioned by other investigators but curiously absent in this series of cases studied, is further evidence of the organic nature of these disturbances.

Failure of disappearance of the leukocytosis, diplopia and muscular tremors following the readministration of morphine when relief was obtained by the addict are difficult to explain. To those who are

8. Garrey, W. E.: Personal communication to the authors.

inclined to accept an emotional basis as the cause of withdrawal symptoms, a satisfactory explanation would be that the craving for the drug brings about emotional states sufficiently powerful to cause organic changes and that readministration of the drug brings mental relief long before the resulting organic changes can rectify themselves. On the other hand, if some true organic disturbance is the basis of the suffering, the readministration of morphine brings about relief from the peripheral sensations just as morphine relieves the patient from the pain of cancer but not from the cancer itself.

CONCLUSIONS

Abrupt withdrawal of morphine for a period of twenty-four hours in four addicts resulted in the appearance of mild withdrawal symptoms. These symptoms were accompanied by negligible changes in the pulse rate, leukocyte count and basal metabolic rate. Changes in behavior and irritability would indicate that mental suffering begins before physical suffering.

In ten addicts, abrupt withdrawal of morphine for a period of forty-eight hours resulted in the appearance of severe withdrawal symptoms. One case showed diplopia. These changes were accompanied by a definite leukocytosis in eight of the ten cases, concentration of the blood in all cases and a slight rise in cholesterol of the blood in seven of the ten cases. Albuminuria was found in two cases. The p_H of the blood, urea nitrogen and sugar showed no changes. Considerable loss of weight occurred during the forty-eight hour withdrawal period.

Following the readministration of the drug and relief from subjective symptoms, the increased leukocyte count and concentration of the blood remained for several hours, as did the diplopia and muscular twitchings of the face. A rise in the percentage saturation of the oxygen of venous blood was noted in all cases following the readministration of the morphine. The circulatory changes noted were a slight increase in the pulse rate and a slight fall in systolic pressure. The staircase climbing test and Schneider's test showed a decrease in the efficiency of the circulation following the readministration of the drug when compared to the results obtained at the end of the forty-eight hour withdrawal period.

THE REGULATION OF BLOOD SUGAR IN IDIOPATHIC STEATORRHEA (SPRUE AND GEE-HERTER'S DISEASE)

I. THE LOW BLOOD SUGAR CURVE *

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The numerous investigations of the rise of blood sugar in the alimentary tract that have been carried out since the introduction of the micromethod for the determination of blood sugar have aimed chiefly to settle the borderline between the normal and the increased rise of blood sugar. The lack of rise or the small rise in blood sugar, the low blood sugar curve, on the other hand, has not attracted any particular attention. In the past year we have had occasion to investigate some instances of the low blood sugar curve. We believe it appropriate to call attention to these curves as constituting a somewhat overlooked phenomenon in the study of the regulation of blood sugar. We have found the low blood sugar curve most frequently present in one definite group of lesions, the idiopathic steatorrheas.

Our examinations of the blood sugar curve after ingestion of dextrose were made as follows:

The blood sugar was determined after the method of Hagedorn and Norman-Jensen. The amount of dextrose ingested was usually 60 Gm. In our first experiments, the blood was withdrawn at intervals of fifteen minutes; in the later experiments, the blood was taken every ten minutes, as we realized that frequent estimations of the blood sugar are important in determining the rise of the curve.

Although there are numerous reports on the rise of the blood sugar curve in normal persons after the ingestion of dextrose, it still has been difficult to find a fairly large number of observations that we could use in arriving at a definition of the term "low blood sugar curve." For such observations, to afford a control of value in our work, had to meet the following requirements: (1) the method employed in the blood sugar determinations had to be the same as that used in our experiments; (2) the amount of dextrose ingested could not differ to any extent from that given our patients, and (3) the intervals between

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* From the Medical Department, St. Elizabeth Hospital, Copenhagen, Physician-in-Chief: T. E. Hess Thaysen.

the withdrawals of blood in any series had to be the same as those in our experiments. The first condition and the last were, of course, the most important.

Investigations of the rise of the blood sugar curve in normal persons after the ingestion of dextrose by the method of Hagedorn and Norman-Jensen have been reported by Hagedorn,[1] Høst,[2] Lottrup-Andersen and Hansen.[3] As is well known, the rise of the blood sugar curve varies considerably in normal persons, and this variation follows the ordinary curve of error in the various observations. We therefore calculated the mean value of the rise of the curve and the mean error, by which we were able to estimate how often a curve of a definite height would be encountered in normal persons.

TABLE 1.—*Calculation of the Low Blood Sugar Curve and Its Frequency in Normal Persons After the Ingestion of Dextrose from the Observations of Hagedorn, Høst, Lottrup-Andersen and Hansen*

Author	Number of Persons	Number of Tests	Mean Value of Rise, Mg. per 100 Cc.	Mean Error	Amount of Dextrose Ingested, Gm.	Interval Between Tests, Minutes	Rise of 60 Mg. per 100 Cc. or Less Calculated Present, per Cent of Tests	Rise of 40 Mg. per 100 Cc. or Less Calculated Present, per Cent of Tests
Hagedorn*	20	39	75	20	47-100	15	25	5
Høst	21	27	74	20	50	15	25	5
Lottrup-Andersen†	18	18	62	12	35	10	45	5
Hansen	5	19	61	16	30-100	2-5	50	10

* Hagedorn's material consisted of two groups: a larger group of fourteen normal persons and a smaller group of six persons with metabolic disorders in their family histories. Here these groups are added together, since no other author made this distinction among normal persons.

† Lottrup-Andersen's normal (?) persons were elderly people, most of them more than 60 years old.

In Lottrup-Andersen's investigations, the amount of dextrose ingested was small, and the same statement holds for some of Hansen's experiments, in which the rise of the curves is calculated after a mean curve that does not include the small increases of the blood sugar values. In Hagedorn's, Høst's and Lottrup-Andersen's material, we find a calculated frequency of a rise of 40 mg. per hundred cubic centimeters or less in 5 per cent of the curves. In Hansen's material, on the other hand, this rise is found in approximately 10 per cent of the curves, which probably is due to the fact that this author calculated the rise from mean curves, not from the values obtained.

1. Hagedorn, H. C.: Undersøgelser over blodsukkerregulationen hos mennesket, Copenhagen, Gyldendal, 1921.

2. Høst, H.: J. Metab. Research **4**:315, 1923.

3. Hansen, K. M.: Investigations on the Blood Sugar in Man, Copenhagen, Nielsen and Lydiche, 1923.

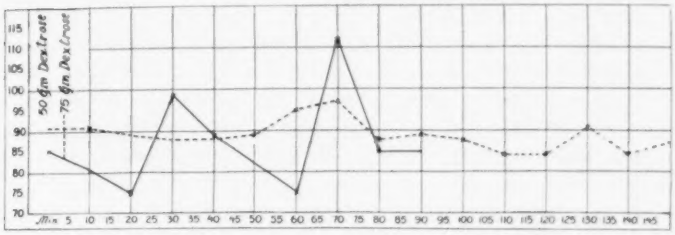

Chart 1.—The blood sugar curves of a woman, aged 33, with nontropical sprue, after ingestion of dextrose (Holst's case). The broken line indicates total rise of 6 mg. per hundred cubic centimeters (Nov. 9, 1926); the unbroken line, total rise of 27 mg. per hundred cubic centimeters (July 2, 1928).

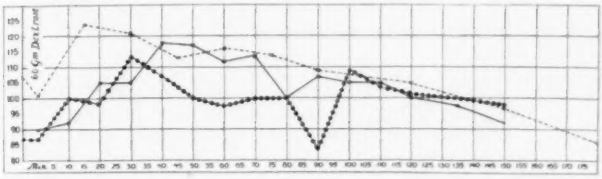

Chart 2 (case 2, table 2).—Blood sugar curves of A. B., a woman, aged 45, with nontropical sprue, after ingestion of dextrose. The broken line indicates total rise of 20 mg. per hundred cubic centimeters (Oct. 26, 1927); the unbroken line, total rise of 28 mg. per hundred cubic centimeters (Jan. 6, 1928); the dotted line, total rise of 27 mg. per hundred cubic centimeters (Feb. 7, 1928).

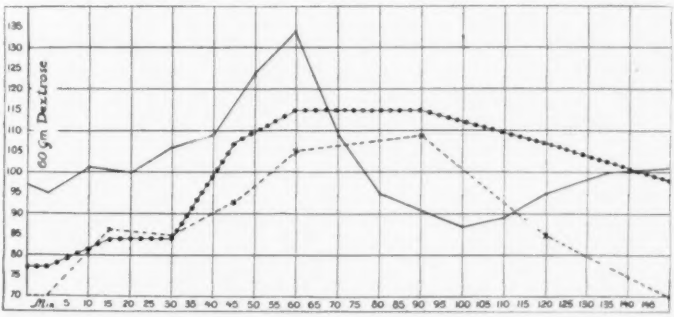

Chart 3 (case 4, table 2).—Blood sugar curves of E. H., a woman, aged 38, with nontropical sprue, after ingestion of dextrose. The broken line indicates total rise of 39 mg. per hundred cubic centimeters (Nov. 2, 1926); the dotted line, total rise of 38 mg. per hundred cubic centimeters (Nov. 3, 1926); the unbroken line, total rise of 37 mg. per hundred cubic centimeters (Jan. 21, 1928).

According to this calculation (table 1), the low curve then is encountered in 5 per cent of normal persons, granted that it is defined as a curve with a rise of 40 mg. per hundred cubic centimeters or less, and provided that the blood is withdrawn at intervals of from ten to fifteen minutes, that the amount of dextrose ingested is approximately 60 Gm. and that the blood sugar is determined after Hagedorn and Norman-Jensen's method.

The low curve is characterized by the small height of its rise. One may also find a low-leveled curve that is characterized by a low starting point during fasting and a relatively low maximal value. We give some illustrations of such low curves demonstrated in cases of idiopathic steatorrhea.

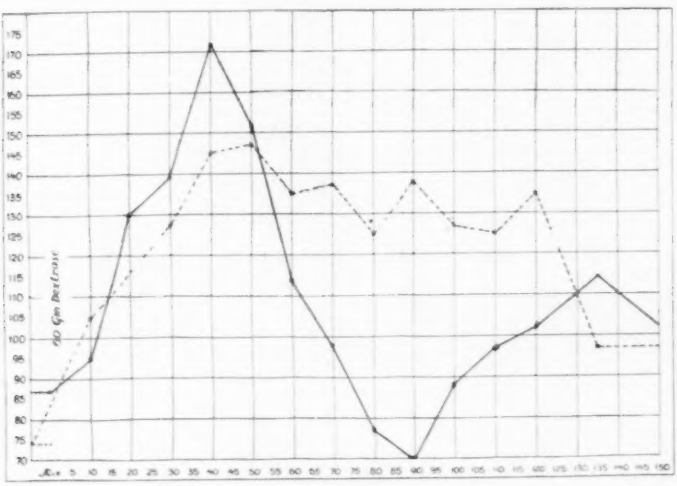

Chart 4 (case 8, table 2).—Blood sugar curves of S. V., a woman, aged 56, with nontropical sprue, after ingestion of dextrose. The unbroken line indicates total rise of 84 mg. per hundred cubic centimeters (Jan. 27, 1928); the broken line, total rise of 73 mg. per hundred cubic centimeters (Feb. 28, 1928).

In the group of diseases designated "idiopathic steatorrhea," we include the following three: (1) tropical sprue, (2) nontropical sprue and (3) the lesion described by Gee [4] (1888) as "celiac affection" and by Herter [5] (1908) as "intestinal infantilism." The reasons for placing these three diseases together in one group and for this designation of the group will not be discussed in this paper. The low blood sugar

4. Gee, S.: St. Bartholmew's Hosp. Rep. **24**:17, 1888.

5. Herter, C. A.: Intestinal Infantilismus, New York, The Macmillan Company, 1908; Wien, Franz Deuticke, 1909.

curve here described is a symptom common to these diseases. This has not been pointed out before.

In a previous article on four cases of nontropical sprue, one of us (Thaysen [6]) emphasized that this lesion sometimes presents certain abnormalities of the blood sugar curve, i. e., a very low rise of the curve after ingestion of dextrose. This observation was later confirmed by Holst,[7] who pointed out that a slight rise of the blood sugar

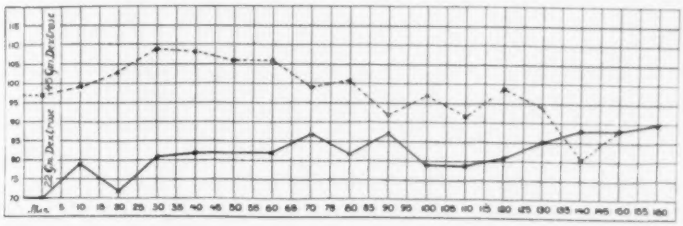

Chart 5 (case 9, table 2).—Blood sugar curves of E. P., a girl, aged 11, with Gee-Herter's disease, after ingestion of dextrose. The unbroken line indicates total rise of 15 mg. per hundred cubic centimeters (Feb. 25, 1928); the broken line, total rise of 12 mg. per hundred cubic centimeters (Feb. 26, 1928).

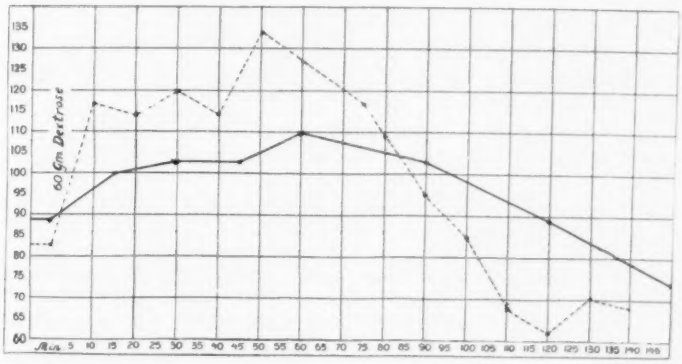

Chart 6 (case 10, table 2).—Blood sugar curves of V. Ø., a man, aged 47, with tropical sprue, almost symptom-free, after ingestion of dextrose; slight alimentary glycosuria was noted; threshold approximately 130. The unbroken line indicates total rise of 21 mg. per hundred cubic centimeters (Aug. 12, 1927); the broken line, total rise of 51 mg. per hundred cubic centimeters (March 1, 1928).

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6. Thaysen, T. E. H.: Acta med. Scandinav. **66**:292, 1926. Exact data on the blood sugar curve are available in only three of the four cases.

7. Holst, I. A.: Acta med. Scandinav. **66**:74, 1927.

curve after ingestion of dextrose evidently is a phenomenon that occurs in nontropical sprue more frequently than was assumed in the paper mentioned.

In the last two years, we have had an opportunity to examine two of the cases of nontropical sprue previously reported, and to investigate the blood sugar curves in four new cases of this lesion, in four cases of tropical sprue and in one case of Gee-Herter's disease (furnished by Prof. C. E. Bloch).[8] Thus, our material consists of twelve cases of idiopathic steatorrhea in which the blood sugar was investigated. To this is added the case reported by Holst.

Table 2 gives a survey of all the cases of idiopathic steatorrhea, including determinations of the blood sugar, the weight and the height of the patients and the results of the analysis of the stools. In regard to the technic in the determination of the metabolism, an article by Thaysen[6] may be consulted.

Whereas one may expect to find a low blood sugar curve in about 5 per cent of normal persons, we found a low blood sugar curve in fifteen of thirty (50 per cent) patients examined who had symptoms of idiopathic steatorrhea (tables 2 and 4).

Of the sixty-four normal persons examined by Hagedorn, Høst, Lottrup-Andersen and Hansen, four presented a low curve on one examination. Six of our eleven patients with idiopathic steatorrhea showed a low curve as an almost constant symptom, for two of our thirteen patients (nos. 11 and 13) must be regarded as having recovered. The low curve thus occurred much more frequently in this group than in the normal groups.[9]

Two of the patients (table 2, nos. 3 and 10) were examined twice, at intervals of one-half year and one month, respectively; each was

8. Another patient with Gee-Herter's disease, recently admitted to the same department, showed likewise a low blood sugar curve after the ingestion of 32 Gm. of dextrose; the total rise was 13 mg. per hundred cubic centimeters of blood. Dr. E. Svensgaard furnished us with the results of these examinations. In a case of Gee-Herter's disease, Esp (Arbeider fra Rikshospitalets med. Aidelinger, Oslo, 1927) found a rise of 39 mg. per hundred cubic centimeters of blood.

9. Although the difference between the frequency proportion of 5 per cent for normal persons and that of 50 per cent for the steatorrheic group is conspicuous, the small number of persons examined might yet give rise to some doubt as to whether the difference is real. By calculating the mean error of the percentages given, this difference is found to be real.

$$\sqrt{\frac{5 \times 95}{100}} + \sqrt{\frac{50 \times 50}{30}} = 11.2$$

To be real, the difference in the percentage of frequency between the groups with low curves (i.e., 50%—5%=45) must be at least twice as large as the figure (11) obtained after this formula; and so it is. Consequently, the difference in frequency is an actual difference.

TABLE 2.—*Survey of Cases of Idiopathic Steatorrhea*

No.	Diagnosis	Age	Sex*	Name	Weight, kg.	Height, Cm.	Date of Determination of Blood Sugar	Amount of Dextrose Administered, Gm.	Time Between Tests, Minutes	Value of Blood Sugar During Fasting, Mg. per 100 Cc.	Maximal Value, Mg. per 100 Cc.	Rise in Mg. per 100 Cc.	Examination of Metabolism	Loss of Fat, Gm.	Loss of Nitrogen, Gm.
1	Nontropical sprue.. (Hoist's case)†	33	♀	.....	25.7	153	9/11/26	50	10	91	95	6	9/ 8/26	50.9	4.3
							9/25/26	75	10	85	112	27			
2	Nontropical sprue‡.	43	♀	A. B.	50.0	161	11/26/27	60	15	104	124	20	11/ 1/27	22.2	2.0
							1/ 6/28	60	10	90	118	28			
							2/ 7/28	60	10	87	114	27			
3	Nontropical sprue¶.	44	♂	M.	50.5	180	8/10/25	50	15	62	89	27	9/ 8/25	25.9	2.1
							1/20/26	50	15	74	115	41			
4	Nontropical sprue#.	38	♀	E. H.	61.7	163	11/ 2/26	60	15	70	109	39			
					63.0		11/ 3/26	60	15	77	115	38			
5	Nontropical sprue..	32	♂	E. N.	51.0	173	1/21/28	60	10	97	134	37	11/19/27	29.8	3.0
							12/19/24	65	15	78	132	54	1/30/24	27.2	1.8
							1/21/26	60	15	65	105	40	11/30/24	28.3	2.8
							2/13/27	60	15	84	142	58			
6	Nontropical sprue..	54	♂	R. S.	57.4	150	1/14/28	60	10	84	134	50			
					50.3		5/29/25	50	10	73	128	55			
7	Nontropical sprue..	57	♀	K. W.	58.2	156	3/ 2/28	60	10	85	138	53	3/ 7/28	66.7	2.7
							10/14/26	100	20	63	152	89	.....	....	1.0
8	Nontropical sprue..	56	♀	S. V.	60.5	161	4/ 4/28	60	10	77	161	84			
							1/27/28	60	10	86	171	85			
9	Gee-Herter's disease	11	♀	E. P.	....	...	2/28/28	60	10	74	147	73	2/25/28	8.7	2.1
							2/25/28	22	10	70	87	17	2/23/28	37.2	2.8
10	Tropical sprue.....	47	♂	V. O.	68.0	185	2/26/28	44	10	97	109	12			
							12/ 8/27	60	15	89	110	21	.....	....	2.0
11	Tropical sprue.....	67	♂	W. S.	62.0	172	1/10/28	60	10	83	134	51			
12	Tropical sprue.....	49	♂	C. A.	88.0	178	12/11/23	88	15	95	162	67	1/26/26	17.7	2.7
13	Tropical sprue.....	36	♂	H. K.	72.5	182	6/ 5/26	50	15	104	184	80	.....	....	4.6

* In this column, ♂ indicates male; ♀, female.
† Microscopic examination showed no increase in fat content of feces.
‡ Microscopic examination showed slight increasse in fat content of feces. Patient had glossitis.
¶ Microscopic examination showed feces normal. Patient had no symptoms.
# Microscopic examination showed slight increase in fat content of feces. Patient had no symptoms.

having a bad period at the time of the first examination and a relatively good period at the time of the second examination. Both showed a considerably higher rise of the blood sugar curve in the relatively good period than in the bad period. Two patients (nos. 7 and 8) with a normal rise of the blood sugar curve were likewise having a good period with normal (no. 8) or only slightly lowered absorption of fat, and without the pernicious anemia and the glossitis that were demonstrated during an attack of fatty diarrhea. Apart from certain nervous symptoms and an abnormality of the basal metabolism which caused us to count them in our total of nonrecovered patients, they were both symptom-free. These observations, together with the experiences before mentioned, indicate that the blood sugar curve becomes normal or rises higher when the patient improves.

In contrast with the normal blood sugar curve, which usually runs a regular course with a smooth fall down to or below the value during fasting, the low curves in idiopathic steatorrhea frequently are irregular in their course (charts 1 to 6), after-rises being not infrequent. These after-rises are encountered at an earlier stage of the curve than is the rule in the curve for normal persons, in which they occur chiefly at the end. In idiopathic steatorrhea, the after-rises are also higher than usual. In one instance (table 2, no. 6, and chart 1), we saw an after-rise of 39 mg. per hundred cubic centimeters, whereas the after-rise in Hagedorn's normal persons amounted to only 10 mg. per hundred cubic centimeters or less. In other respects, however, it is impossible to give any collective description of the low blood sugar curve, as it varies not only among different persons but also in the same person on different examinations.

The length of the curve likewise varies a great deal, when the length is interpreted as the time it takes the curve to get back to the blood sugar value during fasting the first time. In seven cases, the low blood sugar curve got rapidly down to the value during fasting (within ninety minutes or less); but after this, in four of the seven cases an after-rise occurred, which went on to such a slow fall that the curve was not finished until from 151 to 180 minutes after its start. Two other low curves had not reached the blood sugar value obtained during fasting in two and one-half hours after the ingestion of dextrose; and one curve (chart 6) showed a steady rise in blood sugar for two hours—from 70 mg. per hundred cubic centimeters to 90 mg. per hundred cubic centimeters. On the whole, we had the impression that the low curves might be either shorter or somewhat longer than usual.

The blood sugar value during fasting is, on the average, somewhat lower than normal. In our patients, it was approximately 82 mg. per hundred cubic centimeters. It was 88 mg. per hundred cubic centimeters in Hagedorn's patients and 91 mg. per hundred cubic centimeters in

Høst's patients. From table 3, it is evident that the lower average value is due to the fact that blood sugar values of from 60 to 75 mg. per hundred cubic centimeters were more frequent in our patients than in normal persons.

Hypoglycemic values, i. e., values below 70 mg. per hundred cubic centimeters, were found in only three instances and as an inconstant phenomenon.

In two of the cases (table 2, nos. 5 and 6) the blood sugar curve was not low but low-leveled, the blood sugar value during fasting corresponding to the rather low values that were often found in the other curves, whereas the highest value obtained came to only 128 to 142 mg. per hundred cubic centimeters, which is considerably lower than the usual maximal value in normal persons. The entire curve was thus on a lower level than the curves found for normal persons.

It is also worth noticing that the blood sugar value during fasting in those two patients (table 2, nos. 7 and 8) who were examined dur-

TABLE 3.—*Blood Sugar Values, Obtained During Fasting, Arranged in Groups*

Authors	60-75 Mg. per 100 Cc., per Cent of Cases	75-95 Mg. per 100 Cc., per Cent of Cases	95 Mg. per 100 Cc., per Cent of Cases	Number of Cases
Hagedorn, Høst and Hansen.....	5	75	20	143
Thaysen and Norgaard.....	25*	59	16	32

* The usual calculation of the mean error in the percentages of the first group shows that there is a real difference in the frequency per hundred of the values in the group 60-75 mg. per hundred cubic centimeters between Hagedorn's, Høst's and Hansen's patients and ours, as this difference is larger than two times the mean error, which is 9.2.

ing a good period, and whose blood sugar curves showed a normal rise, was relatively low, just as in patients with low curves.

The urine was examined repeatedly during the administration of dextrose. It was found to be sugar-free for all patients but two (table 2, nos. 5 and 10); the urine of these two occasionally gave a faint reduction of Fehling's solution. In view of the fact that Høst found a faint glycosuria in six of twenty-five normal persons after the ingestion of dextrose (50 Gm. dextrose in 200 cc. of water), the slight elimination of sugar in the urine of these two patients hardly seems abnormal.

Finally, we examined the urine of three patients (table 2, nos. 2, 4 and 10) after their ingestion of 100 Gm. of levulose, a test that is recommended by Strauss [10] as a functional test of the liver. Neither Selivanoff's test nor Fehling's solution gave any positive reaction with urine voided one, two, three and four hours after the ingestion of levulose.

The blood sugar curves found for one of the patients (table 2, no. 4, and table 4) are worth mentioning in some detail, because they

10. Strauss, S.: Deutsche med. Wchnschr. **27**:44, 1901.

show that a peculiar change in the curves set in at the same time that the patient showed pronounced signs of latent tetany. We have not found any analogous phenomenon mentioned in the literature.

Thus, the patient had a low blood sugar curve before the appearance of tetany and a normal rise of the blood sugar curve during a period with pronounced signs of tetany (marked facialis phenomenon, increased galvanic reaction, pains in hands and feet, but no convulsions). During this period, the blood sugar value during fasting, too, was considerably higher than before the onset of tetany. On treatment of the patient for tetany with rest in bed, calcium and a preparation of parathyroid, whereby the symptoms were reduced considerably, the blood sugar curve became low once more—lower than before—and the value during fasting went down to the same level as before. During a new period of marked symptoms of tetany, the curve again was higher, and

TABLE 4.—*Blood Sugar in Patient in Whom Signs of Latent Tetany Developed*

Date	Value During Fasting	Rise, Mg. per 100 Cc.	Remarks
11/ 8/26	0.070	39	Fatty diarrhea; no tetany
11/ 4/26	0.077	38	Fatty diarrhea; no tetany
1/21/28	0.097	37	Fatty diarrhea; no tetany
3/13/28	0.091	77	Fatty diarrhea nearly gone; tetany
3/20/28	0.106	89	Fatty diarrhea nearly gone; tetany
4/ 4/28	0.086	21	Fatty diarrhea nearly gone; patient improved; treated with a preparation of parathyroid and calcium
4/17/28	0.105	60	Fatty diarrhea nearly gone; reappearance of tetany in spite of treatment with a preparation of parathyroid and calcium

so was the blood sugar value during fasting. Both curves went down low when the patient improved.

On Nov. 21, 1926, the calcium content of the blood was determined by A. Brems and found to be 10.86 mg. per hundred cubic centimeters, which is a normal value. No more determinations of calcium could be made, as the veins in the arms of the patient were obliterated from numerous venipunctures, and the veins of the legs had been treated with injections for varices.

For that matter, tetany is a rather frequent phenomenon in idiopathic steatorrhea; it was demonstrated in no less than six of the thirteen patients (table 2, nos. 1, 3, 4, 6, 9 and 10). Of the seven patients without a sign of tetany, two (nos. 11 and 12) had recovered from the intestinal lesion, and two others (nos. 7 and 8) had improved considerably. Of the six patients with tetany, five (nos. 1, 3, 4, 9 and 10) had low blood sugar curves; the blood sugar curve of the sixth (no. 6) was really not low but, rather, low-leveled, with a low initial value and a relatively low maximal value. In the patient with Gee-Herter's disease (no. 9), the signs of tetany were present only on a

previous admission to the hospital; tetany could not be made out at the time that the blood sugar curves were examined.

These observations, however, did not give an explanation of the peculiar connection between the manifestation of tetany and the higher rise of the blood sugar in patient E. H. (table 2 no. 4, and table 4). One would rather expect the tetany to be a contributory cause of the low blood sugar curve. This view is supported by the experimental results of Underhill and Blatherwick [11] and Underhill and Nellan.[12] These authors found the blood sugar percentage in dogs falling to 0 after thyroparathyroidectomy. They thought that this hypoglycemia was caused by the absence of the parathyroid glands, since the symptoms of athyreosis subsequent to thyroidectomy do not develop for some time. They also stated that hypoglycemia, after the extirpation, was present before the appearance of tetany. These observations, however, are contested by Hastings and Murray,[13] who could not make out any decrease in blood sugar after the removal of the parathyroid glands. The investigations by Salvesen [14] are also at variance with these results; for he found the blood sugar curve normal in the acute stage of tetany, as well as in the latent stage after parathyroidectomy. Salvesen's curves, however, have the drawback that the determinations of the blood sugar were made at intervals of one-half hour. Salvesen thought that there was some connection between the calcium content of the blood and the tolerance of dextrose in parathyroidectomized animals; for the tolerance was lower when the calcium content of the blood was low. So neither the clinical experiences nor the experimental results give any adequate explanation of the connection between tetany and the rise of the blood sugar curve.

There is no demonstrable connection between the height of the blood sugar curve and the duration of the disease; but, apart from this, it is difficult to obtain any usable information about how long the patients have had steatorrhea. The blood sugar curve in patient 2 (table 2) was extremely low in spite of the fact that he had not definitely had steatorrhea more than one-half year, whereas the curves of patients 5 and 6 showed a higher rise, although they had suffered from steatorrhea for four years, at least.

We attach considerable importance to the rise of the blood sugar curve as a diagnostic aid in the classification of the diseases that come under the head of chronic steatorrhea. In the pancreatogenic form, we find a diabetic curve as the result of a lowered function of the pancreatic islands. There are exceptions, but in eight cases of pan-

11. Underhill, F. P., and Blatherwick, N. R.: J. Biol. Chem. **18**:87, 1914.
12. Underhill, F. P., and Nellans, C. F.: J. Biol. Chem. **48**:557, 1921.
13. Hastings, A. B., and Murray, H. A.: J. Biol. Chem. **44**:233, 1921.
14. Salvesen, H.: Acta med. Scandinav., (supp. 6), 1923, p. 1.

creatogenic steatorrhea we saw only one in which there was a normal blood sugar curve. In alcoholic steatorrhea, the curve either is normal or shows a marked rise followed by a fall to hypoglycemic values. As shown by Meulengracht,[15] in this condition the blood sugar value may drop to 0.033 mg., or even down to 0.001 mg. per hundred cubic centimeters.

How the matter stands in enterogenic steatorrhea from tuberculosis of the mesenteric lymph glands has not yet been studied so far as we know.

The frequent appearance of the low blood sugar curve in sprue is of further importance in connection with the question, still under discussion, whether sprue is related to or identical with pernicious anemia (Elders[16]). As the blood sugar curve in the latter, according to Johnsson[17] and Meulengracht and Iversen,[18] is most frequently normal or increased, one assumes that these observations are against such a relationship.

A later report will deal with some investigations of how the low blood sugar curves develop. For the present, it may be stated that for a number of patients with idiopathic steatorrhea the respiratory quotient before and after the ingestion of dextrose has shown that the dextrose is absorbed and metabolized. Thus, the low blood sugar curve cannot be due to any disturbance of absorption, which would otherwise be an explanation, as the chief symptom of these diseases, the fatty diarrhea, is due to impaired absorption of the fats in the food.

SUMMARY

The term "low blood sugar curve" has been proposed and defined as a curve with a rise of 40 mg. per hundred cubic centimeters or less.

The frequent occurrence of low blood sugar curves in idiopathic steatorrhea (tropical sprue, nontropical sprue and intestinal infantilism) has been pointed out, and its differential diagnostic significance has been mentioned.

A case of nontropical sprue has been described, in which the low blood sugar curve became normal at the same time that the patient showed signs of tetany.

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15. Meulengracht, E.: Acta med. Scandinav. (supp. 26), 1928, p. 181.
16. Elders, C.: Indische Spruwes, Gravenhage, 1918.
17. Johnsson: Acta med. Scandinav. (supp. 3), 1922, p. 139.
18. Meulengracht, E., and Iversen, Poul: Deutsches Arch. f. klin. Med. **148**:1, 1925.

FURTHER OBSERVATIONS ON THE CONTOUR OF NORMAL AND OF TUBERCULOUS CHESTS*

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The shape of the normal and that of the tuberculous chest are so strikingly different that a study of their diameters proves very interesting. A few years ago, while examining chests at the University dispensary, it appeared to me that the tuberculous chest was not flat, as is still a common belief, but rather round. This led me to carry on a series of measurements on normal and tuberculous chests, and I reported my observations in *The Journal of the American Medical Association* in 1927.[1]

Since that time I have made further observations on the contour of normal and of tuberculous chests and shall report them at this time. To make myself clearer, however, I shall give a brief review of my previous report.

The thoracic index, which is the ratio of the anteroposterior diameter to the transverse at the nipple line, was found to be greater in the tuberculous than in the normal chests. In 140 patients in whom a definite diagnosis of pulmonary tuberculosis was made, the average thoracic index was found to be 75.9 per cent, while in 166 students of the University of Minnesota, the average thoracic index was only 68 per cent.

The chests of ninety-nine normal school children and of fifty-one children at Glen Lake Sanatorium were measured. The average thoracic index for the normal children was found to be 71.6 per cent, and the thoracic index for the Glen Lake children was found to be 74.3 per cent.

In twenty-five cases of bronchial asthma and chronic bronchitis occurring in adults, the average thoracic index was 82.8 per cent; an interesting group of patients, forty in all, who came to the University dispensary with ailments of the chest, but who on physical and roentgen examinations disclosed no definite pathologic processes, showed an average thoracic index of 71.4 per cent.

These figures tend to show that the normal chest is approximately 11 per cent flatter than the tuberculous chest and 20 per cent flatter than the chests of persons with chronic bronchitis and asthma.

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* Read before the Southern Medical Association, Rochester, Minn., Oct. 3, 1928.

* From the Department of Medicine, University of Minnesota Medical School, and the Glen Lake Sanatorium, Oak Terrace, Minn.

1. Weisman, S. A.: Contour of Normal and Tuberculous Chests, J. A. M. A. **89**:281 (July 23) 1927.

The chests of children also show a definite difference.

The vital capacity averaged 4,300 cc. in the normal students and 2,650 cc. in the tuberculous patients.

In this paper, I shall report two further observations: the length-width index and the length-depth index. The length-width index is the ratio of the width of the chest to the length, and the length-depth index is the ratio of the depth of the chest to the length. The length of the chest was measured from the lower border of the tenth rib to the upper margin of the outer third of the clavicle about 2 inches (5.08 cm.) outside of the nipple line. The width and the depth of the chest were taken at the nipple line. An ordinary pelvimeter was used graduated with a centimeter scale.

Just one hundred years ago Chomel [2] observed the difference between the shape of normal and of tuberculous chests. Hutchinson,[3] in 1897, and again in 1903,[4] made a careful study of normal and tuberculous chests and showed not only that the tuberculous chest is rounder, but that it is narrower and deeper, and that it is a premature, undeveloped thorax, one approximating that of the quadruped type.

The chest of the fetus is deeper than it is wide, as shown by the investigations of Müller [5] and Hutchinson. A gradual development takes place until birth, as shown by Scammon and Rucker,[6] when the chest is almost round with a thoracic index of 86 per cent. With the establishment of respiration it rises to 106 per cent, and it is about the third month before the thoracic index reaches the measurement it had at birth.

The chest gradually changes in shape, becoming flatter, until about the twentieth year, as shown by a careful study by Zeltner.[7] The vital capacity is greatest at this age, as shown by Stewart.[8] From this time on the chest begins to change and assume a more rounded form until development ceases, in about the sixtieth year, as shown by Weisenberg.[9]

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2. Chomel: Mensuration du thorax, Gaz. d. hôp. **1**:213, 1828-1829.

3. Hutchinson, Woods: Some Deformities of the Chest in the Light of Its Ancestry and Growth, J. A. M. A. **29**:512 (Sept. 11) 1897.

4. Hutchinson, Woods: Is the Consumptive Chest Flat? J. A. M. A. **40**:1196 (May 2) 1903.

5. Müller, Charlotte: Zur Entwicklung des menschlichen Brustkorbes, Morphol. Jahrb. **35**:591, 1906.

6. Scammon, R. E., and Rucker, W. H.: Changes in the Forms and Dimensions of the Chest at Birth and the Neonatal Period, Am. J. Dis. Child. **21**:552 (June) 1921.

7. Zeltner, E.: Thorax Studien, München. med. Wchnschr. **66**:1407, 1919.

8. Stewart, C. A.: The Vital Capacity of the Lungs of Children in Health and Disease, Am. J. Dis. Child. **24**:451 (Dec.) 1922.

9. Weisenberg, quoted by Zeltner (footnote 7).

In 1904, Malone [10] showed by pantographic tracings that the healthy chest was wider and flatter than the tuberculous chest, and that in two chests of the same size, the one with a low thoracic index has a greater cross-sectional area and a greater vital capacity, as shown in figure 1.

From these facts one may assume that the chest of a person 21 years of age, having the diameter measurements of a child's chest is, in all probability, undeveloped. It is this type of chest which is more often associated with tuberculosis. I believe this to be true, as I will tend to show from a study of various diameters of the chest in a fair number of cases.

In order to check the results of my first report, I measured a new group of normal and tuberculous chests. This series consists of 443 students of the University of Minnesota and 316 patients from the Glen Lake Sanatorium; 132 females and 184 males. The children and the patients with asthma are the same as those measured before.

RESULTS

Length-Width Index in Men.—For normal chests I measured 443 students of the University of Minnesota. The average length-width index was 78.4 per cent. This average, however, is over 9 per cent smaller than that shown in Hutchinson's series (85.5 per cent) of less than 100 cases.

The length-width index in my series of 184 tuberculous men was 77.1 per cent. This figure is also less than that (79.9 per cent) shown in Hutchinson's series of only nineteen tuberculous patients and that of Draper's [11] series (87.6 per cent) of seventy-five cases.

Hutchinson's results show that tuberculous chests are about 6 per cent narrower than normal chests, while in my series a difference of only about 1.7 per cent is shown. After I determined the probable errors in the normal and tuberculous series I found that the actual difference, in terms of probable error between the length-width index in normal and in tuberculous chests was only 2.5, which is perhaps not of great significance.

Length-Width Index in Women.—The length-width index in 132 cases of tuberculous chests in women was slightly less than that in men, namely, 76.1 per cent. Draper's series of twenty-eight cases showed an average length-width index of 77.1, which is a difference of only about 1 per cent. From these figures, it appears that the tuberculous chest of a woman is narrower than that of a man.

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10. Malone, F. R.: The Relation of Chest Contour to Lung Capacity, J. A. M. A. **43**:783 (Sept. 17) 1904.

11. Draper, George: Human Constitution, Philadelphia, W. B. Saunders Company, 1924.

Length-Depth Index in Men.—The length-depth index, which is the ratio of the depth of the chest to the length, showed a marked difference between normal and tuberculous chests. The length-depth index for the students averaged 52.5 per cent and for the tuberculous men, 59.7 per cent. The difference is 14.8 in terms of probable error, which is very significant. These figures tend to corroborate the observations of the thoracic index in my previous report, namely, that the healthy chest is the flat one, not the tuberculous chest.

Hutchinson's and Draper's series of cases, which have been mentioned before, show the length-depth index to be even deeper. Malone's series, too, showed that the length-depth index was greater in the tuberculous than in the normal person, as shown by a typical tracing (fig. 1).

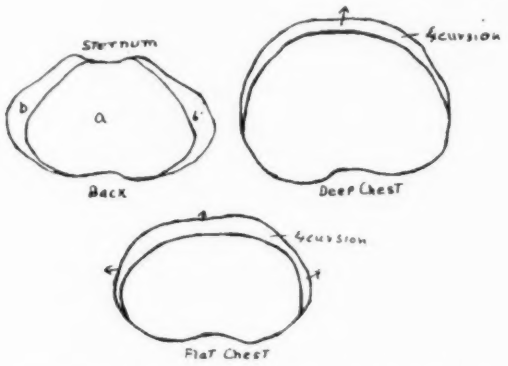

Fig. 1.—Pantographic tracings from Malone. In the tracing of the sternum *a* represents the deep chest and *b* the flat chest.

Length-Depth Index in Women.—In an examination of 132 tuberculous chests in women, the length-depth index averaged 58.2 per cent, while in Draper's series of twenty-eight cases it was 64.7 per cent. Draper's series showed the chest of a woman to be deeper, while my series show the reverse. Draper's series, however, consisted of only twenty-eight cases. Rodes,[12] too, stated that in the negro the female thorax is rounder than the male thorax.

These measurements, therefore, show that the tuberculous chest of the adult tends to be narrower and definitely deeper than the healthy chest (fig. 2).

Measurements of Children's Chests.—The same group of ninety-nine Bremer school children was used for measurements of normal chests and fifty-one children from the Glen Lake Sanatorium for abnormal chests.

12. Rodes, C. B.: The Thoracic Index in the Negro, Ztschr. f. Morphol. u. Anthrop. **9**:102, 1906.

The average length-width index for the chests of fifty-four normal boys was 82.6 per cent, while that of the twenty-four abnormal chests was 84.8 per cent. Here the abnormal chest was the wider by 2.5 in terms of probable error. The same thing was found in the chests of girls. The length-width index for the normal child was 83 per cent and for the abnormal child 85.9 per cent, a difference of 2.9 in terms of probable error. This is probably more significant because of the fact that the average age of the abnormal children is less than that of the normal children by about two years.

There was, however, a noticeable difference in the length-depth indexes between the children in the normal and abnormal groups. The

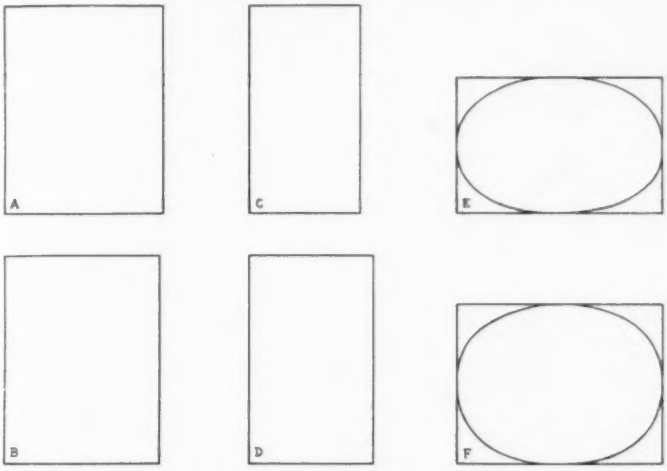

Fig. 2.—Diagramatic sketch of chest diameters. *A* represents the length-width index of the normal chest; *B*, the length-width index of the tuberculous chest; *C*, the length-depth index of the normal chest; *D*, the length-depth index of the tuberculous chest; *E*, the thoracic index of the normal chest and *F*, the thoracic index of the tuberculous chest.

normal boys showed an average length-depth index of 59.3 per cent, while that of the abnormal boy was 62.6 per cent, a difference of 3.1 in terms of probable error.

The chests of the girls showed even a greater difference. The average length-depth of the normal girl was 58.6 per cent and that of the abnormal girl was 64.3 per cent, a difference of 6.9 in terms of probable error.

These children, although a diagnosis of active tuberculosis was not positively made in every case, showed a definitely deeper ch[illegible]an the normal school children.

Bronchial Asthma and Chronic Bronchiectasis.—There were eleven men and fourteen women with bronchial asthma and chronic bronchiectasis. The average length-width for the men was 82.2 per cent, a difference of about 6 per cent from the normal, but only about 1 in terms of probable error. The significant difference, however, is again in the length-depth index which is about 31 per cent or 4.5 in terms of probable error.

The average length-width index for the cases occurring in women is 76.4 per cent, and the length-depth is 59.9 per cent.

In Draper's series of sixteen cases of asthma, consisting of five men and eleven women, the length-width index for the men was 86.4 per cent and for the women 90.7 per cent; the length-depth index for the men was 78 per cent and for the women 70.7 per cent.

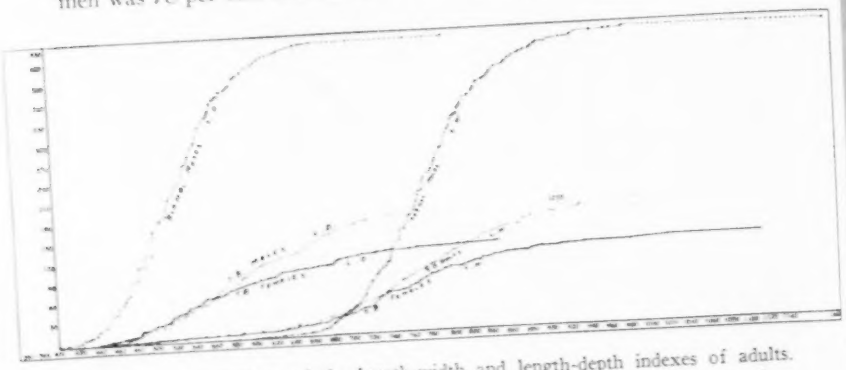

Fig. 3.—Comparison of the length-width and length-depth indexes of adults. The chests of 443 normal men and of 187 tuberculous men and 130 tuberculous women were measured.

From the figures thus far shown in this report and a close study of figure 3, one cannot help coming to the conclusion that the deep, narrow, round chest is more frequently associated with tuberculosis than the flat, wide one.

Respiratory diseases of the nose and throat are important factors in hindering the proper development of the chest (Hofbauer[13]). Chronic diseases, chronic bronchitis and asthma in early childhood also play an important rôle in affecting the proper development of the chest.

COMMENT

I should like to emphasize again the importance of measuring the chests of children as a routine so as to be able to select those children

13. Hofbauer, Ludwig: Mund- und Nasenatmung in ihrem Einfluss auf die Thoraxbewegung. Arch. f. d. ges. Physiol. **147**:271, 1912.

Summary of Indexes of Thoracic Measurements

Type	Thoracic Index 67.27*	Length-Width Index	Length-Depth Index	Average Deviation			Probable Error			Difference in Terms of Probable Error	Age	
				Thoracic Index	Length-Width	Length-Depth	Thoracic Index	Length-Width	Length-Depth		Range	Average
Normal men	66.96	78.42	52.47	4.75	5.04	4.15	±0.202	±0.214	±0.177	.....	15 yr.-47 yr.	19 yr.-2 mo.
Tuberculous men	77.30	77.09	59.73	7.41	7.71	7.08	±0.431	±0.486	±0.462	Thoracic Index = 22.0 Length-width = 2.5 Length-depth = 14.8	18 yr.-80 yr.	36 yr.-9 mo.
Tuberculous women	72.10	76.05	58.20	5.76	8.21	7.39	±0.542	±0.687	±0.561			
Normal children												
Male	72.4 71.9†	82.55	59.28	4.46	3.90	4.02	±0.567	±0.510	±0.450	.....	7 yr.-15 yr.	9 yr.-11 mo.
Female	70.8	82.99	58.59	4.31	5.01	4.50	±0.525	±0.610	±0.529	.....		
Tuberculous children												
Male	73.63	84.75	62.64	5.90	5.85	6.91	±1.03	±0.978	±0.974	Thoracic Index = 1.45 Length-width = 2.1 Length-depth = 3.14	4 yr.-15 yr.	8 yr.
Female	74.88	85.88	64.34	5.00	4.32	3.60	±0.830	±0.765	±0.644	Thoracic Index = 4.18 Length-width = 2.9 Length-depth = 6.9		
Chronic bronchitic asthma												
In men	.....	82.2	68.8	....	8.17	8.12	.....	±1.98	±1.84	Thoracic Index = 9.4 Length-width = 1.0 Length-depth = 3.4		
Both men and women.	82.83	.....	.....	10.58	....	....	±1.63					
In women	.....	76.4	59.9	....	5.60	6.99	.....	±1.53	±1.71			

* 605 cases, including first series.

† Deducting the tuberculous suspect.

who show a chest that appears underdeveloped. This being done, proper exercises such as climbing ladders backward, climbing ropes and trees, work on parallel bars, gymnasium rings, baseball and tennis are desirable. Götz [14] found that under the proper management and exercises the vital capacity of the lungs increased.

CONCLUSIONS

1. The tuberculous chest appears to be round, deep and narrow.

2. The healthy chest tends to be flat and wide.

3. There is evidence that exercise in early childhood can help to develop properly the undeveloped chest.

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14. Götz, H.: Modification of Child Chest by Gymnastics, Monatschr. f. Kinderh. **30**:97 (May) 1925.

SUGAR TOLERANCE IN ARTHRITIS

I. CHRONIC INFECTIOUS ARTHRITIS *

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Dietetic treatment for patients with chronic arthritis has exercised the minds of investigators and clinicians for many years. For a considerable time, it was believed that the proteins constituted an undesirable part of the diet of an arthritic patient. It was felt that an excess of uric acid in the blood was responsible for many conditions of the joints. This conception persisted until Garrod [1] demonstrated that in gout alone, of all the rheumatic conditions, there was a definite excess of any protein metabolite in the blood. In spite of this, there is still considerable confusion as to the rôle that the proteins play in the causation of disease of the joints. It may be stated at this time that, with the possible exception of those rare cases in which a definite food sensitization is present and is demonstrable by skin tests, the protein metabolism is normal in chronic arthritis.

In 1920, Pemberton and Foster [2] reported a diminished sugar tolerance in most cases of chronic infectious arthritis. They further demonstrated that the more severe the arthritis, the more diminished was the tolerance for dextrose. These observers also found that there was an increase in sugar tolerance after the removal of foci of infection, and concluded that the diminished sugar tolerance present in these cases was intimately associated with the presence of focal infection. Their observations were corroborated, in 1922, by the investigations of Fletcher [3] who found a diminished sugar tolerance in a large majority of his cases of chronic infectious arthritis described by him as the "periarticular arthritis of McCrae." He was unable to demonstrate, however, that the decrease in sugar tolerance in these cases was related to the severity of the disease.

* Submitted for publication, Dec. 5, 1928.

* From the Cornell Clinic and the Medical Department of the Cornell University Medical College.

1. Garrod, A. B.: Med. Chir. Tr. London **25**:83, 1848.

2. Pemberton, R., and Foster, G.: Studies on Arthritis in the Army Based on Four Hundred Cases: III. Studies on the Nitrogen, Total Fat and Cholesterol of the Fasting Blood, Renal Function, Blood Sugar and Sugar Tolerance, Arch. Int. Med. **25**:243 (March) 1920.

3. Fletcher, A. Almon: Dietetic Treatment of Chronic Arthritis and Its Relationship to the Sugar Tolerance, Arch. Int. Med. **30**:106 (July) 1922.

Since the initial work of Pemberton and Foster, the low carbohydrate diet has been in vogue with clinicians generally. This type of diet has been employed by me in the Cornell arthritis clinic for the past five years. After some time, it became apparent that the obese, middle-aged women who had the arthritis of the menopause were considerably helped by a restriction of their carbohydrate intake, but that the undernourished patients who had chronic infectious arthritis were unaffected by this form of treatment or, as happened more frequently, were made definitely worse by reduction of their caloric intake. The latter were often underweight to begin with, and a low carbohydrate diet produced in them a state of physical exhaustion without any compensating relief from their joint symptoms.

TABLE 1.—*Clinical Data on Twenty Cases of Chronic Infectious Arthritis*

No.	Name	Sex	Age	Weight, Pounds	Height, Inches	Average Weight, Pounds	Blood Pressure	Duration	Severity
1	D. R.	F	32	135½	60	121	120/80	2 years	Moderate
2	A. K.	F	46	109	59¼	128	104/60	6 months	Mild
3	C. R.	M	53	165	64⅜	148	154/94	2 years	Severe
4	E. E.	F	36	133½	61½	129	120/70	4 years	Severe
5	S. E.	F	37	104⅝	62	127	120/80	5 years	Severe
6	V. F.	F	30	218	62½	127	114/60	18 months	Mild
7	J. L.	M	23	130	65⅝	141	120/78	3 years	Mild
8	M. B.	F	47	139	64	141	120/70	Many years	Mild
9	B. McH.	F	50	107	64½	144	104/70	8 years	Severe
10	H. W.	F	47	111⅜	65	146	120/70	6 years	Moderate
11	D. G.	F	26	120½	60⅝	119	110/70	18 years	Mild
12	D. A.	M	57	133	64½	145	110/68	5 years	Moderate
13	F. K.	F	26	106	61⅛	119	110/60	5 years	Severe
14	E. C.	F	27	131	64½	130	110/60	2 months	Moderate
15	M. T.	F	31	150½	66½	139	120/82	1 year	Mild
16	G. V.	M	51	186	68⅜	168	120/80	2 months	Severe
17	J. M. S.	F	30	102	62	124	130/80	3 months	Mild
18	C. N.	F	48	104	62	136	130/90	10 years	Mild
19	L. W.	F	58	108½	57	127	150/80	10 years	Severe
20	M. H.	F	36	120½	57	117	122/80	10 years	Severe

These clinical observations led to an investigation of the sugar tolerance in the two types of arthritis described.[4] Forty cases were selected as a basis for this study: twenty cases of the arthritis of the menopause and an equal number of the chronic infectious type. These cases were all typical and presented the characteristic signs and symptoms of their group. This report is confined to a consideration of the infectious type.

As previously described,[5] chronic infectious arthritis is primarily a disease of early adult life, and manifests itself as a migratory, polyarticular condition of the joints, characterized by swelling, pain and stiffness of the parts affected. The fusiform finger joint presents the typical picture. As seen in table 1, there were sixteen women and four

4. Cecil, R. L., and Archer, B. H.: Classification and Treatment of Chronic Arthritis, J. A. M. A. **87**:741 (Sept. 4) 1926.

5. Cecil, R. L., and Archer, B. H.: Chronic Infectious Arthritis, Am. J. M. Sc. **173**:258 (Feb.) 1927.

men in this series. The average age was 39½ years, the average weight 130.8 pounds (5.9 Kg.), and the average height 5 feet 2½ inches (1.59 meters). The normal weight for patients of this age and height is 133.8 pounds (6 Kg.). The patients in this group were slightly underweight. The mean systolic blood pressure was 119 mm., and the mean diastolic pressure 74 mm. Two of the patients had a systolic pressure of 150 or more, but only one had a diastolic pressure of more than 90. One of the patients was found to have hyperthyroidism with a basal metabolic rate of plus 20. In one other case there was a suggestion of an endocrine dyscrasia. It has been shown that obesity,[6] hypertension[7] and endocrine dyscrasia[8] may influence the blood sugar curve. A study of the foregoing data shows that few of the extraneous factors that may influence the sugar tolerance were operative in this series.

METHOD

The dextrose tolerance test was conducted according to the method of Hamman and Hirschman.[9] The patient came to the clinic on the morning of the test without any breakfast. At 9 a. m., samples of blood and urine were obtained, and the patient was given 100 Gm. of dextrose and 200 cc. of water. At 9:30 a. m., samples of blood and urine were taken. At 10 a. m., this procedure was repeated, and the patient was given 200 cc. of water. At 11 a. m., samples of blood and urine were obtained and the patient was again given 200 cc. of water. At 12 m., the final samples of blood and urine were collected. All of the patients were given the dextrose by mouth as the intravenous route was felt to be impracticable and undesirable in this investigation. Lennox[10] showed that there was a general correspondence in the results obtained when using both the ingestion and intravenous methods of administering dextrose. Both Pemberton and Fletcher used the alimentary method in their research into this problem.

For the quantitative determination of the blood sugar the Benedict[11] modification of the Lewis-Benedict[12] method was used throughout. The tests were conducted in the Cornell Clinical Pathological Laboratory under the supervision of

6. Paullin, J. E., and Sauls, H. C.: Study of the Glucose Tolerance Test in the Obese, South. M. J. **15**:249, 1922.

7. O'Hare, J. P.: Glucose Tolerance Test in Chronic Vascular Hypertension, Am. J. M. Sc. **159**:369 (March) 1920. Herrick, W. W.: Hypertension and Hyperglycemia, J. A. M. A. **81**:1942 (Dec. 8) 1923.

8. Janney, N., and Isaacson, J.: The Blood Sugar and Thyroid and Other Endocrine Diseases: The Significance of Hypoglycemia and the Delayed Blood Sugar Curve, Arch. Int. Med. **22**:160 (Aug.) 1918.

9. Hamman, L., and Hirschman, F. L.: Alimentary Hyperglycemia and Glycosuria as a Test for Sugar Tolerance, Arch. Int. Med. **20**:761 (Nov.) 1917.

10. Lennox, W. D.: Blood Sugar, Arch. Int. Med. **40**:182 (Aug.) 1927

11. Benedict, S. R.: Note on the Determination of Blood Sugar by the Modified Picric Acid Method, J. Biol. Chem. **37**:503, 1919.

12. Lewis, R., and Benedict, S.: A Method for the Estimation of Sugar in Small Quantities of Blood, J. Biol. Chem. **20**:61, 1915.

Dr. Thro. In their original work Pemberton and Foster employed this method exclusively and found it satisfactory and well adapted for this type of investigation. Fletcher used the Folin and Wu[13] technic for blood sugar determination.

COMMENT

The results of the tests are given in table 2.

The mean level during fasting in this series was 0.108 per cent. Half an hour after the ingestion of the dextrose, the mean reading for the group was 0.146 per cent. At the end of an hour, this figure was lowered to 0.139 per cent; at the end of two hours, it was 0.119 per cent; after three hours, the curve dropped to 0.102 per cent. The highest

TABLE 2.—*Observations on the Blood and Urine*

	Blood Sugar, Mg. per 100 Cc.					Urine Sugar				
No.	Fasting	½ Hour	1 Hour	2 Hours	3 Hours	First Test	Second Test	Third Test	Fourth Test	Fifth Test
1	107	125	115	100	75	0	0	0	0	0
2	100	150	125	100	75	0	0	0	0	0
3	107	125	150	136	115	0	0	0	0	0
4	100	150	150	125	100	0	0	0	0	0
5	107	150	125	100	100	Slightly reduced	Slightly reduced	+	0	0
6	100	150	136	100	...	0	0	0	0	0
7	125	166	150	125	120	0	0	0	0	0
8	100	150	125	115	100	0	0	0	0	0
9	100	150	125	100	90	0	0	0	0	0
10	107	150	136	107	100	0	0	0	0	0
11	115	150	...	187	150	0	0	0	0	0
12	120	166	150	150	125	0	0	0	0	0
13	10.	125	115	75	60	0	0	0	0	0
14	107	125	150	125	107	0	0	0	0	0
15	115	150	136	125	115	0	0	0	0	0
16	125	166	187	136	120	0	0	0	0	0
17	88	125	136	100	75	0	0	0	0	0
18	125	166	136	100	100	0	++	++	0	0
19	115	133	166	150	115	0	0	0	0	0
20	100	150	136	125	107	0	0	0	0	0

level during fasting in the series was found to be 0.125 per cent and the lowest level 0.088 per cent. The maximum concentration in any one case after ingestion of the dextrose was 0.187 per cent. The minimum response was 0.125 per cent. Glycosuria was present in only two cases of the entire series.

To interpret properly the significance of the curves obtained it is necessary to set a normal standard. The question of what constitutes a normal surgar tolerance curve involves two factors, namely, its height and its extent. Various observers have given diverse figures as their conception of the maximum normal percentage of the sugar concentration in the blood after the ingestion of a test load of dextrose.

13. Folin, O., and Wu, H.: A System of Blood Analysis: I. A Simplified and Improved Method for the Determination of Sugar, J. Biol. Chem. **41**:367 (March) 1920.

Jacobsen,[14] MacLean and de Wesselow,[15] Fletcher,[3] and Spence[16] considered 0.17 per cent as the upper postprandial limit in normal subjects. On the other hand, Hamman and Hirschman,[9] Pemberton,[2] and Hopkins,[17] believed that 0.15 per cent is the normal maximum concentration after giving dextrose. Still other observers have reported much higher figures. Goto and Kuno[18] found that the average fasting blood sugar concentration during fasting of 0.092 per cent rose to a maximum of from 0.125 to 0.185 per cent after the ingestion of dextrose, while Sakaguchi[19] gave from 0.133 to 0.191 per cent as the figures for the upper normal limit.

With so much discrepancy as to the maximum normal range following a test load of dextrose, it remained for Gray[20] to collect 452 sugar tolerance curves in clinically normal subjects and set a normal standard. This he did by analyzing 300 curves of this group which had been obtained after feeding 100 Gm. of dextrose or its equivalent. As the standards set by other observers are based on relatively small groups of cases, Gray's conclusions are important. The study of his 300 curves shows that the normal range is between 0.11 and 0.16 per cent, but that there is a large range of higher values. In his series of 452 curves obtained after giving various test loads of dextrose, sixty-five, or 14 per cent of the group, showed a maximum value of more than 0.17 per cent. In the group of 300 subjects given 100 Gm. of dextrose, thirty-eight, or 13 per cent, gave a maximum concentration of more than 0.17 per cent. This means that in one of seven curves there is apt to be a peak above 0.17 per cent, even in a series of clinically normal subjects. Gray, however, considered sugar tolerance peaks of more than 0.17 per cent as abnormal and, as he stated, "the definition of the import of values of

14. Jacobsen, A.: Untersuchungen über den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, zuckerkranken, und graviden Personen, Biochem. Ztschr. **56**:471, 1913.

15. MacLean, H., and de Wesselow, O. L. V.: The Estimation of Sugar Tolerance, Quart. J. Med. **14**:103 (Jan.) 1921.

16. Spence, J. C.: Some Observations on Sugar Tolerance, with Special Reference to Variations Found at Different Ages, Quart. J. Med. **14**:314 (July) 1921.

17. Hopkins, A. H.: Studies in the Concentration of Blood Sugar in Health and Disease as Determined by Bang's Micro-Method, Am. J. M. Sc. **149**:254 (Feb.) 1915.

18. Goto, K., and Kuno, N.: Studies on Renal Threshold for Glucose, Arch. Int. Med. **27**:224 (Feb.) 1921.

19. Sakaguchi, K.: Beitrage zur Diabetesforchung. Erste Mitteilung. Ueber den Einfluss von Menge, Art und Zeit der Kohlenhydratzufuhr auf den Blutzuckergehalt beim gesunden Menschen, Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, **20**:345, 1918.

20. Gray, H.: Blood Sugar Standards, Arch. Int. Med. **31**:241 (Feb.) 1923.

0.17 per cent and over can justly be made only in the future when the after-history of these or similar exceptional subjects shall have been reported."

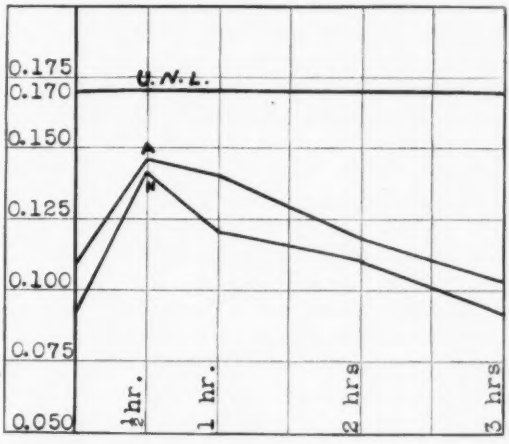
Fletcher took this figure as the upper normal limit, but Pemberton and Foster considered 0.15 per cent as the acme of blood sugar concentration after the feeding of 100 Gm. of dextrose. As their conclusions were based on the examination of only eight normal subjects, it was felt advisable in this investigation to adopt the standard set by Gray.

Hamman and Hirschman,[9] in their original report, stated that after the ingestion of 100 Gm. of dextrose, the resulting curve should return to normal in from two to three hours. This is conceded by practically all observers. MacLean and de Wesselow [15] found that the extent of the curve depended on the amount of dextrose given. When 25 Gm. are fed to a normal subject, the curve drops to the predextrose level in ninety minutes; when 50 Gm. are used, in about two hours, and, with greater amounts, in from two to three hours. Spence [16] also showed that the return to normal of the sugar tolerance curve depended on the age of the patient. There is a tendency in older subjects to have a higher and more prolonged curve.

If a postprandial reading of blood sugar of more than 0.17 per cent is considered to be an evidence of a diminished tolerance for dextrose, one finds that only two cases, or 10 per cent of the series, fall into this category. In case 11, the maximum concentration reached was 0.187 per cent. This was the figure for two hours; the figure for one hour is unavailable, because insufficient blood was obtained to perform the test. It is reasonable to suppose that the figure for one hour would have been even higher than 0.187 per cent. As the curve was still at 0.15 per cent after three hours, this case was definitely one of diminished sugar tolerance. It is interesting to note that this was a mild case of chronic infectious arthritis, although one of long duration. Case 16 likewise showed a high maximum concentration (0.187 per cent), but the return to the predextrose level was made in three hours. This was a case of severe infectious arthritis of short duration in a man, aged 51.

Three cases, or 15 per cent of the group, had a normal peak, but the curve failed to return to the predextrose level in three hours. In patient 3, aged 53, with a predextrose level of 0.107 per cent the reading was still 0.115 per cent after three hours. In case 12, the reading ranged from a fasting level of 0.12 per cent to 0.125 per cent after three hours. In patient 20, aged 36, with a concentration during fasting of 0.1 per cent, the reading was 0.107 per cent in three hours. The average difference in the two levels in the three cases was only 6 mg. per hundred cubic centimeters. The average age was 49, which probably accounts for the slight variation from the normal. However, patient 20, aged only 36, may be considered to have had a slightly diminished sugar tolerance.

Only one case (11) of the entire series showed both a maximum concentration of more than 0.17 per cent and a failure of the curve to return to the predextrose level in three hours. Including case 16, with a maximum concentration of more than 0.17 per cent and case 20 (a patient, aged 36) in which the curve failed to return to normal in three hours, there were three cases, or 15 per cent of the series, with abnormal curves. This corresponds rather closely with the observations of Gray [20] who reported departures from the normal in 13 per cent of his series. In the accompanying chart is seen the mean curve of the entire series as contrasted with the mean curve of Gray's 300 normal patients who were submitted to the same test.



Average curve for the series, contrasted with the normal curve of Gray. *N* represents the normal curve; *A*, the average curve, and *U.N.L.*, the upper normal limit (0.170 per cent) as established by Gray.

The predextrose level of the present series (0.108 per cent) is considerably higher than that of Gray's (0.09 per cent). This may be due to the higher average age of the group. Gray failed to give the average age in his series of cases, although Spence showed that the age factor is important in interpreting the results for sugar tolerance. In the present series, the average maximum concentration after the feeding of dextrose was 0.146 per cent as contrasted with the normal maximum of 0.14 per cent. The normal increase in blood sugar concentration, however, one-half hour after giving 100 Gm. of dextrose, is 0.05 per cent. In this group the average increase one-half hour after the test load was only 0.038 per cent. As the level for the half hour is usually the maximum figure obtained, this tends to indicate that a greater tolerance was present

in the series than in normal subjects. In one hour, the normal figure is 0.03 per cent above the predextrose level, and in the arthritic group it is 0.031 per cent. The normal curve returns to its original level in three hours. In this group there was a slight drop below the predextrose level, a phenomenon which has been found to be a common occurrence in normal subjects.[21]

Although the presence of postprandial glycosuria as a test for sugar tolerance has been discarded, it is interesting to note that only two patients, or 10 per cent of the series, showed glycosuria after the ingestion of 100 Gm. of dextrose. This is in marked contrast with the normal figure established by Gray, who found that 40 per cent of 129 normal patients showed glycosuria after a similar test load of dextrose.

Pemberton and Foster expressed the belief that the sugar tolerance in chronic infectious arthritis varies directly with the severity of the disease. They found that the more severe the arthritis, the more diminished was the tolerance for dextrose. As shown in table 1, there were eight mild cases in the present series, four that were considered moderate and eight in which the process was thought to be severe. The mean maximum reading in the mild cases was 0.157 per cent; the average rise from the predextrose level was 0.049 per cent. In only one case was there failure to return to the original level in three hours. The average peak in the moderate cases was 0.148 per cent; the average rise from the predextrose level was 0.037 per cent. In one case, there was a slight increase over the predextrose level after three hours. In the eight severe cases the average maximum reading was 0.153 per cent; the postdextrose rise was 0.046 per cent. In two of the cases, the curves failed to return to the predextrose level in three hours, but in one of these the patient was 53 years of age and there is little significance to the slight discrepancy present. As already mentioned, case 20 (a patient, aged 36) may be considered as showing a slightly diminished sugar tolerance. The highest average peak, and the highest average increase in blood sugar concentration after a test load of dextrose were both found to be present in the mild cases. The severe cases showed lower peaks and the moderate cases the lowest average blood sugar concentration of the three groups. In each of the three categories, there was one case in which the curve failed to return to normal in three hours. It is apparent from these observations that there is no relationship between the sugar tolerance and the severity of the arthritic process. This is in accord with the observations of Fletcher.[3]

21. Folin, O., and Berglund, H. J.: Some New Observations and Interpretations with Reference to Transportation, Retention and Excretion of Carbohydrates, J. Biol. Chem. **51**:213 (March) 1922. Leifmann, E., and Stern, R.: Ueber Glykaemia und Glykosurie, Biochem. Ztschr. **1**:299 (July 18) 1906.

Pemberton and Foster [2] also demonstrated a relationship between foci of infection and sugar tolerance. Their observations were corroborated by Pringle and Miller,[22] and more recently by Evans, Riding and Glynn.[23] The original observers found that the removal of definite foci of infection was followed soon after by an increase in the tolerance for dextrose. In the present series, foci of infection were demonstrable in eighteen of the twenty cases (table 3). In five cases more than one focus of infection was present. Diseased tonsils, alone or in combination with other foci, were the source of infection in fifteen, or 75 per cent, of the cases. Apical abscesses, alone or in combination with other foci, were present in five cases, or 25 per cent of the series. Pyorrhea, both mild and moderate, was found in a number of patients, but was not thought severe enough to be considered as a source of infection. The proportion of cases of tonsillar infection to those of infection of the

TABLE 3.—*Foci of Infection and Their Relationship to the Sugar Tolerance Test*

No.	Name	Foci Present at Time of Test	Foci Removed Before Test	No.	Name	Foci Present at Time of Test	Foci Removed Before Test
1	D. R.	None	Tonsils	11	D. G.	Tonsils	None
2	A. K.	Tonsillar stubs, teeth	None	12	D. A.	Sinuses, epididymis	None
				13	R. K.	None	Tonsils
3	C. R.	None	Tonsils	14	E. C.	None	Tonsils
4	E. E.	Tonsils	None	15	M. T.	Tonsils	None
5	S. E.	None	Tonsils, teeth, cervix	16	G. V.	Prostate, tonsils	None
6	V. F.	Tonsils, cervix	None	17	J. M. S.	Sinuses	None
7	S. L.	Teeth	Tonsils	18	C. N.	None	Teeth
8	M. B.	None	None	19	L. W.	Tonsils	Teeth
9	B. McH.	Bronchi	None	20	M. H.	Tonsils	None
10	H. W.	Tonsils	None				

teeth is a little higher in this group than in the larger series of cases of infectious arthrititis reported a year before the present article. Other organs considered to harbor foci were: the sinuses (two cases), the cervix (two cases), and the prostate, epididymus and bronchi (one case each).

All of these cases were active, and the patients were under treatment at the clinic. None could be considered as belonging to the group which Pemberton and Foster in their report called "convalescent." As shown in table 3, active foci were present at the time that the sugar tolerance test was performed in thirteen, or 65 per cent, of the cases. Original foci had been removed but the disease was still active at the time the test was given in six cases, or 30 per cent of the series. In two cases, original foci had been removed but other foci were present and active

22. Pringle and Miller: Glucose Tolerance in Chronic Arthritis, Lancet **1**:171 (Jan. 27) 1923.

23. Evans; Riding, and Glynn: The Influence of Oral Sepsis upon Carbohydrate Tolerance in Non-Diabetics, Lancet **2**:592 (Sept. 17) 1927.

at the time of the sugar tolerance determination. In one case, there was no demonstrable focus nor did the history throw any light on any original source of infection.

The average maximum blood sugar concentration in the thirteen cases with demonstrable foci was 0.158 per cent. The average predextrose level of this group being 0.108 per cent, it is found that after a test load of dextrose, there was an increase in blood sugar concentration of the exact normal figure (0.05 per cent). The average maximum concentration of the blood sugar in the six cases with evidence of a definite arthritic process but with eradicated foci was 0.144 per cent. The average predextrose level for this group was 0.11 per cent. The average increase in concentration after the ingestion of dextrose was only 0.034 per cent as compared with 0.05 per cent in the former group. This might be interpreted to mean that in cases of infectious arthritis with active foci there is less tolerance for dextrose than in those in which the foci have been eliminated. Against this assumption, however, is the fact that those cases in which foci are active show no deviation from the normal standard as established by Gray. One must conclude, therefore, that there is no definite evidence at hand to prove that focal infection has any specific effect on sugar tolerance.

CONCLUSIONS

1. In a study of twenty typical cases of chronic infectious arthritis, no evidence was found of a diminished sugar tolerance.

2. The sugar tolerance in this disease does not seem to vary with the severity of the process.

3. Foci of infection apparently have no specific action on the sugar storage mechanism.

FRUCTOSURIA *

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REPORT OF CASE

History.—Early in August, 1927, a servant girl, aged 23, was admitted to the medical clinic of the University Hospital at Groningen, Holland, because her physician could not find an appropriate diet after having treated her for three years for a condition he thought was diabetes. Backache was the complaint which led the girl to see a physician, and he had found reducing properties in her urine. At that time, the patient had been drinking a good deal, the quantity of urine passed was abundant and the appetite was normal. A diet was prescribed, from which sugar and sweet foodstuffs were omitted, with potatoes and bread in moderate quantities. The backache disappeared, but the urine was not always sugar-free. The physician further informed us that the urine passed at night never contained any sugar, while that passed during the day at times showed reducing properties.

About a year prior to consulting the physician, the patient had suffered from pleurisy with effusion, and she had been resting several months. No cough or expectoration had been present, and some emaciation only at first.

The personal and family history did not contain any data of special significance; there was no familial tendency toward diabetes.

Examination.—The patient was fairly well nourished, healthy looking and of normal build. She weighed 61.3 Kg. The skin and mucous membranes were normal; the lymph glands were not enlarged. The pulse rate and respirations were not abnormal. The blood pressure was 120 systolic and 75 diastolic (Riva-Rocci technic). The cranial nerves functioned well; the tongue was slightly coated. The teeth showed caries, pyorrhea alveolaris and defects; the tonsils were not swollen. The thyroid was slightly enlarged, and the trachea not displaced. The thorax was moderately arched; the right half was sunken, and there was less expansibility than on the left side. The heart was normal on percussion and auscultation. The lower border of the right lung was a little higher than the left and moved less freely. On the right anteriorly, the percussion note was shorter, with weakened respiration and a few crepitant râles. The abdomen, spine, genitals and extremities did not show any abnormalities. All reflexes were normal. The roentgenogram of the thorax revealed no abnormalities except slight traces of pleurisy and small infiltrations in the right upper lobe. The Pirquet reaction was positive, the Wassermann reaction negative.

The differential leukocyte count was as follows: eosinophils, 1 per cent; neutrophil juvenile forms, 0.5 per cent; band forms, 13 per cent; polymorphonuclears, 50 per cent; lymphocytes, 32 per cent; monocytes, 3.5 per cent.

The sedimentation rate was 22 mm. in the first hour (Westergreen).

The patient, therefore, showed signs of mild pulmonary tuberculosis, for which, after observation in this clinic, she was treated in a sanatorium with excellent results.

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* From the Clinic for Internal Medicine, Prof. Polak Daniels, Director.

The phenomena of a disturbed carbohydrate metabolism deserve special attention. On her admittance, the urine reduced both Fehling's and Nylander's solutions, besides showing a trace of acetone but no diacetic acid. The polarization plane was turned to the left, and our suspicion that the reducing substance was not dextrose but fructose was proved by the following tests:

1. After fermentation, the urine did not reduce the solutions.
2. The urine showed the Seliwanoff reaction.
3. The reaction of Bang [1] was also positive (heating on addition of ox gall and strong hydrochloric acid). It may therefore be safely asserted that the patient excreted levulose with the urine.

LITERATURE AND COMMENT

From the literature, three forms of fructosuria are known:

1. There is a special alimentary levulosuria occurring in conditions of the liver parenchyma, such as hepatic cirrhosis, catarrhal jaundice, hepatic syphilis, etc., to which Strauss [2] first called attention. This alimentary fructosuria has even become a much applied test of liver function. Later, for the estimation of the hepatic function, the galactose test came to be regarded as of great value, although the significance of the first is still highly appreciated by many investigators (for instance, King [3]).

2. It does not seem to be rare in diabetes mellitus, particularly in severe cases, for the patients to excrete not only dextrose, but also fructose, in the urine. Different estimations of the frequency of this condition have been given by various authors. Von Noorden regarded fructosuria in diabetes mellitus as a signum mali ominis.

3. True fructosuria, in the absence of any hepatic disturbance and of diabetes mellitus, is a rare condition, of which so far about fifteen cases [4] have been recorded; and only two of these were investigated with a fair degree of completeness.[5] In this form of fructosuria, levulose is excreted with the urine, if this sugar, as such, or as a constituent of

1. Bang: Lehrbuch der Harnanalyse, Wiesbaden, Bergmann, 1918, p. 119.
2. Strauss: Deutsche med. Wchnschr. **39**:1780, 1913.
3. King, G.: Lancet **1**: 385, 1927.
4. Seegen: Zentralbl. f. d. Med. Wissensch., 1884, p. 753. Külz: Ztschr. f. Biol. **27**:228, 1884. Rosin and Laband: Ztschr. f. klin. Med. **47**:182, 1902. Schlesinger: Arch. f. exper. Path. u. Pharmakol. **50**:1, 1903. Lepine and Boulud: Rev. de Med. **24**:185, 1904. Neuhauer: München. med. Wchnschr. **2**:1525, 1905. Moraczemslci: Ztschr. f. klin. Med. **64**:503, 1907. Adler: Arch. f. d. ges. Physiol., vol. 139, p. 93. Strouse, S., and Friedman, J. C.: Levulosuria, Arch. Int. Med. **9**:99 (Jan.) 1912. Barrenscheen: Biochem. Ztschr. **127**:222, 1922. Snapper, I.; Grünbaum, A., and van Creveld, S.: Nederl. Tijdschr. v. Geneesk. **1**:1600, 1926; also, Arch. f. Verdauungskr. **38**:1, 1926. Steinberg, S., and Elberg, W.: Klin. Wchnschr. **4**:2399, 1925.
5. Barrenscheen and Snapper, Grünbaum and van Creveld (footnote 4).

other carbohydrates (for example, cane sugar), is taken up with the food. If the food is totally deprived of this sugar, its excretion at once ceases. This anomaly, in which fructosuria is the only phenomenon distinguishing the patient from a normal person, should not be called a disease. This metabolic deviation may even go on for years, without unpleasant or disastrous consequences (Adler[6] described the case of a patient, aged 73), so that the prognosis is favorable. In some cases, a familial tendency has been described; in others, this factor was absent. If treatment is desired, it is, as already stated, sufficient to omit from the diet all foodstuffs containing fructose, and equally so those carbohydrates from which, in the intestine, fructose is formed, while other carbohydrates are allowed as desired.

To find out to which group our patient belonged, we had to determine first of all whether the function of the liver was normal. The

TABLE 1.—*Estimation of Liver Function by Galactose Test* *

Time	Blood Sugar, per Cent	Reduction in Urine
Fasting	0.081	0
After ½ hour	0.095	—
After 1 hour	0.092	0
After 1½ hours	0.097	—
After 2 hours	0.089	0

* 40 Gm. of galactose by mouth.

TABLE 2.—*Results of Administration of Fifty Grams of Dextrose by Mouth*

Time	Blood Sugar, per Cent	Glycosuria
Fasting	0.079	0
After ½ hour	0.089	0
After 1 hour	0.125	0
After 1½ hours	0.089	0
After 2 hours	0.082	0

usual methods of physical examination did not give any indication of a damaged function (no enlargement of the organ, no splenomegaly, no jaundice or no increased urobilinuria). Moreover, the liver function was estimated by the galactose test, the results of which are given in table 1.

The urine, voided after one and two hours, did not reduce the solutions. After the administration of 50 Gm. of galactose by mouth, a feebly dextrarotatory urine was excreted, with slightly reducing properties and containing at the most 0.34 Gm. of galactose, a quantity undoubtedly to be regarded as entirely normal. We may therefore assume that in our patient the liver function was sufficient.

Secondly, it was necessary to determine whether this fructosuria was not an accompanying symptom of true diabetes mellitus. The blood sugar during fasting appeared to be entirely normal, equally so the blood sugar curve obtained according to Maclean's technic.

6. Adler (footnote 4).

The alimentary hyperglycemia after the administration of 50 Gm. of dextrose by mouth was particularly low, while the fasting level was reached within the normal time. Even after the administration of 100 Gm. of dextrose by mouth, the rise in blood sugar was not higher than 0.157 per cent, thus relatively low (table 3).

The decline was somewhat slower after 100 Gm. of dextrose had been given: not until after three hours was the fasting level reached. In our case (patient weighing 61 Kg.), 100 Gm. of dextrose (i.e., 1.6 Gm. per kilogram of body weight) was a rather large quantity, so that any disturbance of dextrose metabolism could be excluded.

After proving that there was no disturbance of liver function and no diabetes mellitus, we can safely say that our case belongs to the rare group of cases of essential fructosuria. To understand this peculiar anomaly, one must first consider what happens in the normal organism when fructose is administered.

TABLE 3.—*Results of Administration of One Hundred Grams of Dextrose by Mouth*

Time	Blood Sugar, per Cent	Glycosuria
Fasting	0.091	0
After ½ hour	0.143	0
After 1 hour	0.157	0
After 1½ hours	0.131	0
After 2 hours	0.130	0
After 2½ hours	0.106	0
After 3 hours	0.096	0

Large quantities of fructose may be taken by mouth without a trace of this sugar appearing in the urine. There is, however, a marked difference between the effects from the ingestion of dextrose and of fructose; namely, with fructose there is no increase in the blood sugar. But it is quite certain, that after administration of fructose a slight fructosemia occurs (Isaac,[7] Folin and Berglund [8]).

It is also certain that the liver plays the most prominent part in the storage and transformation of fructose. Isaac [9] discovered that only the unimpaired liver cell is capable of transforming fructose into dextrose (perfusion experiments), while muscles, like the liver, may cause fructose to disappear (glycogenesis, other chemical transversions, combustions, perhaps), but in this case there was no formation of dextrose. Like Folin and Berglund, Isaac believed that the liver cannot store all fructose, and that a part escapes into the blood stream and immediately is stored in the muscles. This occurs more rapidly and more completely with fructose than with dextrose, since in the muscles there is a "vacuum" for fructose, while dextrose is always present.

7. Isaac, S.: Med. Klin. **16:** 1207, 1920.
8. Folin and Berglund: J. Biol. Chem., vol. 51, p. 213.
9. Isaac: Ztschr. f. phys. Chem. **89:** 78, 1914.

The normal organism does not excrete fructose in the urine, although after the administration of fructose by mouth, this sugar in low concentration appears in the peripheral circulation (according to Isaac, from 0.02 to 0.04 per cent). So in human beings there is a threshold value for fructose, the height of which is unknown.

Contrary to what we found in man were the results of the perfusion experiments by Hamburger and Brinkman [10] with frog kidneys. These showed that fructose quantitatively passed over from the perfusion liquid into the artificial urine.

To recall the results obtained by various experimenters with the intravenous administration of fructose in man and animals is confusing. If large quantities of fructose are introduced in this manner, it appears that as great a quantity is excreted by the kidneys as is obtained from a solution of dextrose of the same concentration. This becomes evident from experiments by Wierzuchowsky [11] undertaken for different purposes. About 10 per cent of both sugars was recovered in the urine, while after the infusion of dextrose the rise in blood sugar was much higher than that after the introduction of fructose. Here it becomes strikingly apparent how deficient is one's knowledge of the fate of the various carbohydrates in the body. One imagines that the liver, the muscles and the kidneys behave differently toward fructose than toward dextrose, and yet it is a fact that both sugars in almost perfect correspondence are excreted by the kidneys after intravenous administration. There are so many unknown factors that any explanation so far does not seem more than speculation. Owing to the excellent cooperation of our patient, not only did we succeed in being able to confirm the results obtained by other students of this subject, but we were able also to open up some new vistas, which we believe to be of some importance for a better understanding of this abnormal condition.

EXPERIMENTS

We will now report the results of various experiments performed on our patient.

The amount of sugar in the blood was determined by the modified micromethod of Bang. In most cases, determinations of fructose in the urine were made as well with the polarimeter as with the reduction method of Causse and Bonnans.

On a mixed diet, our patient always excreted a certain quantity of fructose. This excretion ceased at once if all foodstuffs containing fructose were omitted.

10. Hamburger and Brinkman: Proc. Roy. Acad., 1918, vol. 21.

11. Wierzuchowsky: J. Biol. Chem., vol. 68, p. 631.

Fructose was administered by mouth, as follows: 50 Gm. of fructose was given on an empty stomach. The urine was examined every half hour, and the blood sugar every fifteen minutes during the first half hour, and then every half hour; the results are given in table 4.

The same experiment in a normal woman yielded the results shown in table 5.

Contrary to what is normally seen, the administration of fructose caused a significant increase in blood sugar, which reached its maximum after one hour, returning to the fasting level after two and a half hours.

TABLE 4.—*Results of the Administration of Fifty Grams of Fructose by Mouth in Our Patient*

Time	Blood Sugar, per Cent	Fructosuria		
		Polarimeter, per Cent	Polarimeter, Gm.	Reduction, Gm.
Fasting	0.094	0	0	0
After ¼ hour	0.107	—	—	—
After ½ hour	0.116	0.8	0.26	0.30
After 1 hour	0.144	3.9	1.22	1.24
After 1½ hours	0.123	4.5	1.43	1.51
After 2 hours	0.110	2.8	1.74	1.80
After 2½ hours	0.091	1.6	0.60	0.62
After 3 hours	0.096	0.5	0.40	0.42
After 3½ hours	0.095	0.4	0.34	0.27
After 4 hours	0.087	0.2	0.11	0.15
After 4½ hours	0.077	0.1	0.02	—
After 5 hours	0.096	0.1	0.05	0.07
After 5½ hours	0.071	0.2	0.09	—
After 6 hours	.....	0	0	0
Total excretion: 6.32 Gm. = 12.6 per cent			6.26	6.38

TABLE 5.—*Results of the Administration of Fifty Grams of Fructose by Mouth in a Normal Woman*

Time	Blood Sugar, per Cent	Fructosuria
Fasting	0.096	0
After ½ hour	0.103	—
After 1 hour	0.106	0
After 1½ hours	0.107	—
After 2 hours	0.093	0

Fructosuria appeared within the first half hour, i.e., in a period when the rise in blood sugar was still slight (0.023 per cent). It did not reach its maximum until after two hours, when the blood sugar content had been decreasing for a long time; and it still continued for five and a half hours after administration, i.e., for another three hours after the blood sugar level had become normal. So we may conclude that in our case there was practically no threshold for fructose, since this substance appeared in the urine when no more than traces could circulate in the blood. In this respect, our case differed from that of Barrenscheen,[12] who found a well marked threshold for fructose in his

12. Barrenscheen (footnote 4).

case. We have stated that in normal persons a threshold for fructose must be assumed, though being relatively low, so that in this respect our patient differed from a normal person.

In this experiment, the amount of blood sugar was determined only in the fasting condition and after one hour. At this time, fructosemia was determined by the method of Jolles (modified by van Creveld [13]): 1 cc. blood was mixed with 1 cc. of a 4 per cent solution of hydrochloric acid, and then, while it was vigorously shaken, 2 cc. of a 5 per cent solution of mercuric chloride was added by drops; this was followed by centrifugation; 1 cc. of the supernatant fluid was mixed with 1 cc. of a 25 per cent solution of hydrochloric acid. This gave rise to a blue color which was compared with a color scale, obtained by adding different quantities of fructose to normal blood.

TABLE 6.—*Results of the Administration of One Hundred Grams of Pure Fructose by Mouth*

Time	Blood Sugar, per Cent	Fructosuria (Polarimeter)	
		per Cent	Gm.
Fasting	0.048	0	0
After 1 hour	0.134	2.7	1.35
After 2 hours	—	4.05	5.06
After 3 hours	—	4.75	2.00
After 4 hours	—	3.51	1.12
After 5 hours	—	4.56	2.46
After 6 hours	—	1.19	0.67
After 7 hours	—	0.65	0.39
After 8 hours	—	0.24	0.18
After 9 hours	—	0.38	0.15
After 10 hours	—	0.11	0.20
After 11 hours	—	0	0
Total excretion			13.58 = 13.58 per cent

We found in the blood after one hour a fructose content of 0.079 per cent. The total sugar content at the same moment was 0.134 per cent, which corresponds to a rise of 0.086 per cent (calculated as dextrose). Now, 0.079 per cent of fructose has the same reducing power as 0.073 per cent of dextrose, so that of the total rise of 0.086 per cent, 0.073 per cent may be attributed to fructose, and only the remaining 0.013 per cent the result of dextrose. It would seem, therefore, that almost the whole rise in blood sugar is due to fructosemia.

We further administered 142 Gm. of fructose by mouth (2 Gm. per kilogram of bodyweight), from which 19.8 Gm., 13.9 per cent, was excreted. A repetition of the same experiment gave an excretion of 18.2 Gm., 12.8 per cent.

Not only after the administration of relatively large quantities of fructose, but also after minute quantities, fructosuria occurs.

Even after the administration of 2 and of 1 Gm. of fructose by mouth, reducing substances were found in the urine.

13. Van Creveld, Klin. Wchnschr., 1926.

That the excretion is independent of the rapidity with which it is taken up by the body became manifest when 50 Gm. were administered, not in a single dose, but in divided doses.

When fructose was given intravenously instead of by mouth, we obtained the following results:

After the intravenous administration of 20 cc. of an 8 per cent fructose solution (1.6 Gm.), the urine contained fructose for two hours, a total amount of 0.23 Gm., or 14.4 per cent of the injected quantity. From 50 cc. of an 8 per cent solution of fructose (4 Gm.

TABLE 7.—*Results of the Administration of Five Grams of Fructose by Mouth*

Fructose Given	Fructosuria (Polarimeter)	
Time	Per Cent	Gm.
Fasting	0	0
After 1 hour	0.28	0.17
After 2 hours	0.63	0.66
After 3 hours	0.17	0.21
After 4 hours	0	0
Total excretion		1.04 Gm. = 20.8 per cent

TABLE 8.—*Results of the Administration of Fifty Grams of Fructose*

Fructose Given		Fructosuria (Polarimeter)	
Time	Gm.	Per Cent	Gm.
9¾ hours	5	0	0
10¼ hours	5	—	—
10¾ hours	5	0.29	0.61
11¼ hours	10	—	—
11¾ hours	10	1.11	0.89
12¼ hours	5	—	—
12¾ hours	10	1.88	2.07
1¾ hours	..	0.86	1.88
2¾ hours	..	0.46	0.87
3¾ hours	..	0.40	0.72
4¾ hours	..	0	0
Total given	50 Gm.	Total excretion	7.04 Gm. = 14.08 per cent

of fructose), which we injected intravenously, 0.41 Gm. was excreted in the urine (10.2 per cent) in four hours.

In two control experiments, we injected 4 Gm. of fructose intravenously into normal persons. No urine showing reducing properties was excreted in either case.

Table 9 shows the excretion of fructose in the foregoing experiments, in which fructose had been given in various ways and in different amounts.

If one bears in mind the quantity of fructose appearing in the urine when widely varying quantities of fructose are administered by mouth, our case brings out anew the fact observed by other investigators, that, independent of the quantity administered, the excreted amount of fructose

represents a fairly constant percentage of the given dose (about 14 per cent) in all cases. On the administration of 5 Gm. of fructose, the excretion was even greater than after doses of 100 and 142 Gm.[14]

It is logical that our next step would be to ascertain whether the excretion of fructose in our patient was influenced by the hormone, which for the carbohydrate metabolism is of overwhelming significance, namely, insulin. The experiments by Wierzuchowsky brought out that insulin influences only the excretion of dextrose, while the elimination of fructose remains unchanged if both substances are introduced intra-

TABLE 9.—*Results Obtained from the Administration of Fructose*

Method	Fructose Given, Gm.	Fructose Excreted	
		Gm.	Per Cent
By mouth	1.0	+	+
By mouth	2.0	+	+
By mouth	5.0	1.04	20.80
By mouth	50.0	6.32	12.64
By mouth (in refracta dosi)	50.0	7.04	14.80
By mouth	100.0	13.58	13.58
By mouth	142.0	19.00	13.38
Intravenously	1.6	0.23	14.38
Intravenously	4.0	0.41	10.25

TABLE 10.—*Results of the Administration of Insulin*

	Blood Sugar, per Cent	Fructosuria		
		Polarimeter		Reduction, Gm.
		Per Cent	Gm.	
Fasting, 10 units of insulin	0.085	—	—	—
After ½ hour, 50 Gm. of fructose by mouth	0.095	0	0	0
After 1 hour	0.122	—	—	—
After 1½ hours	0.123	1.31	2.15	2.21
After 2 hours	0.117	—	—	—
After 2½ hours	0.111	1.37	3.90	4.27
After 3½ hours	0.102	0.51	1.17	1.35
After 4½ hours	0.107	0.40	0.40	0.45
After 5½ hours	0.107	0.14	0.18	0.24
After 6½ hours	0.108	0	0	0
Total excretion: 8.16 Gm. = 16.32 per cent			7.80	8.52

venously. In perfect harmony with these investigations, in the case of Snapper, insulin did not produce a diminished fructosuria. Table 10 shows that in our case also no action of insulin could be seen.

Earlier observations showed that for the excretion of fructose in persons with fructosuria, it is not immaterial whether the fructose is administered as the only carbohydrate or introduced with other carbohydrates, or whether it is introduced as disaccharide and polysaccharide, respectively. Schlesinger and Barrenscheen reported that under the

14. The fructosuria after the administration of 5 Gm. of fructose by mouth was different from that in all other similar experiments, so we repeated this one with just the same result.

latter conditions more fructose appears in the urine. We gave fructose by mouth in combination with an equal quantity of dextrose and galactose, which are, in contrast to fructose, metabolized in a normal manner. The results appear in tables 11 and 12.

The excretion of fructose was also studied after the administration of 96 Gm. of cane sugar (representing 50 Gm. of fructose).

Under the conditions represented in table 13, a greater part of the fructose was excreted than when fructose was given alone. It is most remarkable that after the administration of cane sugar the fruc-

TABLE 11.—*Results of the Administration of Twenty-five Grams of Fructose and Twenty-five Grams of Dextrose by Mouth*

Fructose Given	Fructosuria (Polarimeter)	
	per Cent	Gm.
Fasting	0	0
After 1 hour	0.63	1.25
After 2 hours	0.85	1.62
After 3 hours	0.63	1.25
After 4 hours	0.28	0.93
After 5 hours	0.23	0.41
After 6 hours	0	0
Total excretion		5.46 Gm. = 21.8 per cent

TABLE 12.—*Results of Administration of Twenty-five Grams of Fructose and Twenty-five Grams of Galactose by Mouth*

Fructose Given	Fructosuria (Polarimeter)	
	per Cent	Gm.
Fasting	0	0
After 1 hour	0.57	1.51
After 2 hours	0.80	1.63
After 3 hours	0.34	0.61
After 4 hours	0.20	0.48
After 5 hours	0.06	0.21
After 6 hours	0	0
Total excretion		4.44 Gm. fructose, 17.8 per cent

tosuria was considerably greater than when fructose and dextrose were given together.

Of more importance than the fructosuria only is the behavior in regard to inulin, the polysaccharide of fructose. Neubauer demonstrated that this substance was not excreted by his patient with fructosuria, contrary to what had been expected. We obtained the same results. Neither did the patient give a reduction in the urine on the administration of 5 or 20 Gm. of inulin. Neubauer pointed out that nothing is known of what happens with the inulin in the intestine. One is inclined to assume that it is converted into fructose, analogous to the breaking up of amylum into dextrose. But this has by no means been proved. On the contrary, many arguments against it may be adduced.

Lewis and Fraenkel [15] found that in dogs in which diabetes has been produced by the administration of phlorizin, an additional amount of dextrose appears in the urine after the administration of fructose, but not following a dose of inulin.

Goudberg [16] did not observe a rise of the respiratory quotient after administering inulin, contrary to the results obtained after giving fructose. The results of Neubauer, corroborated by us, accord perfectly with this. The fact that inulin does not produce fructosuria in a patient who may be regarded as markedly sensitive to fructose is a strong plea for the contention that in the intestine, at any rate, no fructose is formed from inulin.[17]

TABLE 13.—*Results of the Administration of Ninety-Six Grams of Cane Sugar by Mouth*

Time	Blood Sugar, per Cent	Fructosuria		
		Polarimeter		Reduction, Gm.
		per Cent	Gm.	
Fasting	0.058	0	0	0
After 1 hour	0.157	1.43	2.86	2.83
After 2 hours	0.143	2.05	5.14	5.80
After 3 hours	—	1.48	3.25	3.29
After 4 hours	—	2.56	2.85	3.14
After 5 hours	—	1.23	0.68	0.80
After 6 hours	—	0.94	0.32	0.37
After 7 hours	—	0.28	0.14	0.16
After 8 hours	—	0	0	0
Total excretion: 15.81 Gm. = 31.6 per cent			15.24	16.39

The metabolic disturbance in our patient was concerned only with fructose, while dextrose, galactose and mannose were assimilated in a normal manner.

A glance at the structural formula of fructose will reveal that it occupies a place by itself. It is a ketose, while the other sugars are aldoses.

Structural Formulas

H	H	H	H
H-C-OH	H-C-OH	H-C-OH	H-C-OH
H-C-OH	H-C-OH	HO-C-H	H-C-OH
H-C-OH	H-C-OH	H-C-OH	H-C-OH
HO-C-H	HO-C-H	H-C-OH	HO-C-H
H-C-OH	HO-C-H	HO-C-H	C=O
C=O	C=O	C=O	H-C-OH
H	H	H	
Dextrose	Mannose	Galactose	Fructose

15. Lewis and Fraenkel: J. Biol. Chem., 1914, vol. 17.

16. Goudberg: Ztschr. f. exper. Path. u. Therap., vol. 13, p. 310.

17. We could prove the absence of inulin in the urine by finding no reduction on heating in an alkaline medium reaction, by which inulin is easily broken up into fructose.

It is desirable to determine whether the disturbance is due to this difference in structure, that is, whether it depends on the presence of the keto-group. It happens that almost all sugars in nature are aldoses, there being only three known ketoses:

H	H	H
H-C-OH	H-C-OH	H-C-OH
H-C-OH	HO-C-H	H-C-OH
H-C-OH	H-C-OH	HO-C-H
HO-C-H	HO-C-H	HO-C-H
C=O	C=O	C=O
H-C-OH	H-C-OH	H-C-OH
H	H	H
Fructose	Sorbose	Tagatose

Tagatose is a sugar rarely encountered and difficult to prepare. We did not succeed in procuring it. Sorbose is not so rare. It is prepared from the fruit of rowan (*Sorbus aucuparia*). It is levorotatory, and gives, like fructose, the reactions of Seliwanoff and Bang, but does not ferment, by which characteristic it can be differentiated from fructose. Owing to the kindness of Professor Boeseken at Delft, we obtained about 5 Gm. of this hexoketose. We administered 4.8 Gm. in one dose.

TABLE 14.—*Results of the Administration of 4.8 Gm. of Sorbose by Mouth*

		Sorbosuria		
		Polarimeter		
Time	Blood Sugar, per Cent	per Cent	Gm.	Reduction, Gm.
Fasting	0.085	0	0	0
After ½ hour	0.087	—	—	0.11
After 1 hour	0.086	0.88	0.68	0.55
After 1½ hours	0.096	0.54	0.86	0.81
After 2 hours	0.086	0.54	0.54	0.40
After 2½ hours	0.079	0.38	0.30	0.34
After 3 hours	0.076	0.38	0.21	0.23
After 3½ hours	—	0.50	0.25	0.28
After 4 hours	0.093	0.50	0.33	0.25
Each half hour until after 7 hours	—	0.25	0.50	0.65
After 7½ hours	—	0	0	0
			3.67	3.62

Total excretion: 3.67 Gm. sorbose = 76 per cent

The patient appeared to be much more sensitive to sorbose than to fructose. No less than 76 per cent of the administered quantity was recovered in the urine as sorbose, as the negative fermentation test showed.

Our supply was too small for a study of the tolerance of healthy persons, and we must, therefore, rely on the literature on this subject, which from its very nature is meager. Of 3 Gm. of sorbose given by mouth, Cremer [18] could recover 17 per cent in the urine, while after the ingestion of 0.25 Gm. and 1 Gm., respectively, no reduction was obtained.

18. Cremer: Ztschr. f. Biol. **29**:484, 1892.

Voit [19] obtained 36 per cent in the urine, after injecting 10 Gm. subcutaneously. From these figures, and in the absence of other data, we believe the excretion is so much higher than the amount mentioned by the investigators that we feel justified in speaking of an abnormal reaction in our patient toward sorbose. We, therefore, hold that this result, if corroborated by the necessary control tests in healthy persons, may serve as argument for the contention that the presence of the keto-group is of predominating significance for the special place fructose holds among the other sugars studied.

Besides sorbose, we also studied dioxy-acetone, $CH_2OH\text{-}CO\text{-}CH_2OH$, equally a ketose. Our patient, as well as healthy persons, did not excrete this substance in the urine. It is well known that this sugar is much more easily stored by the liver (as glycogen) than all other known higher sugars (Isaac and Adler [20]).

It is not permissible to place this keto-triose on a level with the higher ketoses, and so we must abstain from any conclusion in this respect.

Where in the body is the seat of the metabolic disturbance found, and what is its underlying mechanism?

As to the location of the disturbance, one thinks, first of all, of the organ which, under normal conditions, has the greatest influence on fructose metabolism—the liver. The fact that the administration of fructose by mouth leads to a considerable degree of fructosemia is a strong argument for the assumption that the liver allows more fructose to escape into the blood stream under these circumstances than under normal conditions. A disturbed flow from the circulation toward the muscles (Folin and Berglund) might be considered, but this is a purely hypothetic notion. It is contrary to the facts to assign to the muscles, instead of the liver, a preponderating influence on fructose metabolism, as investigations by Isaac and others have brought out.

A more positive proof that the liver is the primary seat of the disturbance is the fact that the fructosuria is just the same whether fructose is administered by mouth or intravenously. From this we may infer that the influence of the liver on the storing of fructose is extremely slight, contrary to the tendency in normal persons.

It is more difficult to explain the mechanism of this disturbance. In the first place, one must bear in mind the remarkable constancy of the fructose excretion when greatly varying doses are administered. This phenomenon cannot be accounted for by the assumption that there is an insufficiency of a definite function, as in diabetes mellitus. In the latter condition, different quantities would be excreted not only in the

19. Voit: Deutsches Arch. f. klin. Med. **58**:535, 1897.

20. Isaac, S., and Adler, E.: Klin. Wchnschr. **3**:1208, 1924.

same patient, but in different cases. The fact that always the same fraction of the introduced fructose is excreted indicates with certainty that a definite metabolic function has dropped out.

There are two possibilities to be thought of, as Neubauer lucidly reasoned out, but later investigators have paid little attention to them. However scant our knowledge of the normal fructose metabolism may be, it is certain that the greater part of the fructose which the liver gets from the intestine is stored in that organ as glycogen, and that a smaller part passes over into the blood stream, from which it disappears rapidly. We also know that a part of the fructose is at once oxidized. This oxidation process is manifested by a rapid increase in the excretion of carbon dioxide, together with a rise of the respiratory quotient, a phenomenon repeatedly observed.

Neubauer suggested that the disturbance is possibly this: under normal conditions, a definite part is always oxidized, but in patients with fructosuria this oxidation process fails. Neubauer himself had no opportunity to determine the amount of carbon dioxide excretion. We determined the respiratory quotient in our patient twice before, and one hour after, the administration of 142 Gm. of fructose (2 Gm. per kilogram of body weight), with the following results:

	Respiratory Quotient Before	Respiratory Quotient After
Normal person	0.71	0.95
Our patient, first test	0.72	0.77
Our patient, second test	...	0.75

Here one sees striking evidence that a rise in the respiratory quotient, as compared with what is observed in normal persons, is absent; and we may conclude, therefore, that no combustion of sugar takes place.

In a return again to the constant relation between the fructose administered and that excreted, which in all observed cases of fructosuria is of the same value, the question arises whether an analogy is found somewhere else.

Hamburger,[21] in his experiments on the permeability of the glomerulus membrane to stereo-isomeric sugars, found a similar phenomenon. On perfusion of the frog's kidney with Ringer's solution to which various sugars had been added, it was shown that galactose was partially retained. Closer investigation into the permeability of galactose showed that independent of the concentration of the galactose in the perfusion fluid, there is always a fairly constant part, namely, the lesser half, that is passing through. The same occurrence was revealed on perfusion with levoxylose. At once we were impressed by the analogy between

21. Hamburger: Biochem. Ztschr. **128**:185, 1922.

the results of these perfusion experiments and what we found in fructosuria. Hamburger looks for an explanation in the different behavior of the two forms, the α—and β—modification, which together, as equilibrium mixture, form the d-galactose.

From the rotation coefficients of the two forms, their mutual relation may be calculated, and it is shown that the excreted part of galactose corresponds nicely to the quantity of one of the forms.

With regard to fructosuria, we have suggested the possibility that the body is abnormally adapted to one of the two modifications of fructose, and that the organism is not capable of assimilating it in the normal manner. This modification may have a constant value in the equilibrium between the two.

If from the rotation of the two separate forms and the equilibrium one calculates the relation between the α—and β—modification, one finds 37 per cent α-fructose and 63 per cent β-fructose. The amount excreted by our patient (approximately 14 per cent) can, therefore, not be held to consist of only one of the two forms. Howeevr, the possibility must be borne in mind that in vivo the equilibrium is different from that in an aqueous solution, on which our calculations are based. We did not succeed in finding in Ringer's solution a rotation differing from that in water, but in vivo there may be various known and unknown factors that influence this equilibrium. Above all, it should not be forgotten that Hamburger made his perfusion experiments with surviving frog kidneys, whereas we dealt with the complete living human organism.

For the present, no further advance is to be made from mere theoretical speculation. We have, nevertheless, attempted by experimental methods to prove the probability that the mystery of the constant excretion is connected with the equilibrium between the α- and β-fructose.

If fructose as solid substance (i.e., β-fructose) is dissolved, α-fructose in the increasing quantities gradually arises in the solution until after a time equilibrium is established. This phenomenon can be controlled by the polarimeter; rotation of the solution diminishes (so-called multirotation).

We injected intravenously a solution of fructose immediately after its preparation and observed the excretion. A considerably greater part of the fructose appeared in the urine than after the intravenous administration of a solution of fructose dissolved some time prior to injection. On the administration of fructose by mouth, no marked difference is to be expected, since with fructose the equilibrium is established rather quickly (within a half hour), so that when absorption from the intestine is complete, equilibrium has already been established. This observation can be explained only by the assumption that the disturbance found in our patient is bound up with one of the two modifications.

There is a second argument, pointing in the same direction, namely, that the excretion of the fructose depends on the simultaneous presence of other sugars. It is plausible that under those conditions other equilibriums arise than with fructose alone. The same holds good for cane sugar, from which fructose is not formed until it has reached the gastro-intestinal tract.

With the same question in view, we finally introduced crystalline fructose through the rectoscope as high into the rectum as possible. Of 17.5 Gm., 7.7 Gm. (44.4 per cent) was excreted with the urine.

This is a considerable difference, but we do not believe it to be of great importance on account of the manner in which the fructose was introduced. Theoretically, there is considerable indication in the results of our experiments that the metabolic disturbance in fructosuria is particularly associated with one of the two forms of fructose.

TABLE 15.—*Results of the Intravenous Injection of 7.7 Gm. of a Solution of Fructose Immediately After It Was Prepared*

	Fructosuria	
Time	Polarimeter, Gm.	Reduction, Gm.
Fasting	0	0
After ½ hour	0.89	0.92
After 1 hour	0.28	0.23
After 1½ hours	0.13	0.13
After 2 hours	0.06	∞
From 2½ until 5 hours	0.16	0.12
After 5½ hours	0	0
Total excretion: 1.46 Gm. = 19 per cent	1.52	1.40

It would be of great interest to examine the urine immediately after its formation in the kidneys with regard to the phenomenon of multirotation. We did not consider ourselves justified in carrying out the necessary cystoscopy and ureteral catheterization.

We saw that not only fructose, but also sorbose, is excreted for the greater part with the urine of our patient, and that from the literature it is known that this rare sugar is the only one of all known sugars that, when ingested by normal persons, passes over into the urine. We believe that a more profound investigation of the manner in which the excretion takes place, and, in particular, a quantitative examination under varying conditions might lead to important results. The difficulty in obtaining a sufficient quantity of sorbose is the only obstacle.

In our patient, the fructosuria was encountered as an isolated metabolic disturbance, since, apart from a mild pulmonary tuberculosis, she did not show any pathologic anomaly. She did not present any other sign of constitutional deficiency, nor of disturbance in the organs of internal secretion, as has been reported by other investigators in similar cases. Mentally she was entirely normal. Hereditary tendencies were

totally absent and, so far as known, there were no other cases of fructosuria in her relatives. Of her near relatives (father, mother, brother and sister), we had the opportunity to examine the urine voided after the ingestion of a fairly large quantity of cane sugar. Reducing substances were not found. Cases of diabetes mellitus or of other disturbances of metabolism were not encountered in the relatives. So there was nothing in our case pointing to an hereditary constitutional anomaly. Nevertheless, on the ground of other cases reported in the literature, we have to assume such a constitutional factor.

Of great interest is the idea of van Creveld, who suggested the possibility of the fructosuria being a remnant of fetal life. He found that new-born children, particularly premature children, have less tolerance to fructose. This tolerance of fructose, according to him, develops slowly during fetal life, and if it does not arise, fructosuria results.

When the function of the liver is otherwise intact, a partial decrease in tolerance to fructose is never met with (that is, a true fructose-diabetes), but either a normal reaction toward this sugar or the typical picture of fructosuria. This fact, we believe, speaks strongly against van Crevald's hypothesis.

Resuming, we find that fructosuria is, from many points of view, a remarkable disturbance of metabolism, though harmless in character.

That so far our insight into the essential nature of this condition is but dim is, in the first place, due to the great rarity of the anomaly. But when we have the opportunity, with the complete and admirable cooperation of the patient, to examine such a case, we are, in our attempts at interpreting the results of various experiments, continually handicapped by the great gaps in our knowledge of the normal metabolism of fructose. Notwithstanding, we do believe that our observations have shed more light on a few points thus far in utter darkness.

SUMMARY

An extensive investigation was made in a case of true (essential) fructosuria, and the following facts were determined:

1. Fructosuria disappears at once, if only food, free from fructose, is consumed.

2. Independent of the quantity of fructose administered, a fairly equal part of it is excreted by the urine (about 14 per cent).

3. Contrary to the results under normal conditions, the administration of fructose leads to a considerable rise of the blood sugar content, due almost entirely to fructosemia.

4. After the administration of fructose in divided doses, as much is excreted as when fructose is given in a single dose.

5. The intravenous introduction of fructose produces fructosuria of the same degree as administration by mouth.

6. Insulin has no influence on the fructosuria.

7. Fructose, given in combination with other sugars or as a polysaccharide, results in a more severe fructosuria than when nothing else is given.

8. Inulin does not produce fructosuria, probably because it is not broken up in the intestine into fructose.

9. The metabolism of dextrose, galactose, maltose and mannose is not disturbed.

10. Sorbose (a ketose like fructose), the only known sugar that is normally excreted in small quantities in the urine, was excreted in large quantities in the urine in our case. The keto-group was probably responsible for this metabolic disturbance.

11. After the administration of fructose, there is no rise of the respiratory quotient, contrary to what is seen in normal conditions.

12. Fructose injected into the vein immediately after the solution has been prepared leads to a greater degree of fructosuria than the intravenous introduction of a solution prepared some time prior to the injection.

13. Crystalline fructose, administered by rectum, produces a more severe fructosuria than fructose given by mouth.

14. A connection probably exists between the last two results (nos. 12 and 13) and the phenomenon of multirotation.

HYPERINSULINISM

REPORT OF TWO CASES *

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Since the introduction of insulin in treatment, the symptoms of hypoglycemia have become well known. Many cases are being recognized in which hypoglycemia occurs spontaneously. As a rule, the symptoms are mild, but in a small number of cases they have been severe. The increasing incidence of the disorder and the serious disability which sometimes results make careful investigation highly important.

REPORT OF CASES

Three cases in which there was a constant tendency to severe hypoglycemia have been observed at the Mayo Clinic. I reported the first case (case 1) about two years ago in collaboration with Wilder, Power and Robertson.[1] The patient had attacks of loss of consciousness, with convulsions, if he failed to receive sugar every hour during the day and night. It was demonstrated that hypoglycemia was due to overproduction of insulin from carcinoma of the islands of the pancreas

CASE 2.—A farmer, aged 52, came to the Mayo Clinic in August, 1928, because of attacks of weakness and stupor which had occurred at intervals for more than two years. On many occasions he had lost consciousness and had had convulsions. He noted that the attacks were most likely to occur if he had gone without food for several hours, or if he undertook any exertion. He found that eating would relieve or prevent the symptoms, so he formed the habit of taking food at frequent intervals. A curious incident in the history is that early in the course of the trouble he fell into a stuporous state which persisted for a week. Because a trace of sugar had been found in the urine previously, diabetic coma was suggested, although glycosuria was not observed at this time. Insulin was given for ten days, probably in small doses. The patient was able to swallow liquid nourishment such as eggnog and orange juice, and was fed liberally. He regained consciousness gradually. As time went on, the patient had to take larger amounts of food at shorter intervals. For several months before admission, he had been obliged to eat at bedtime and during the night. He was unable to work; slight exertion, such as mowing his lawn, often precipitated attacks. Even when resting, failure to take sufficient food resulted in attacks several times a week. The patient's condition was considered hopeless.

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* Read before the Central Society for Clinical Research, Chicago, Nov. 23, 1928. The work was done in the Division of Medicine, the Mayo Clinic.

1. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas; Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348 (July 30) 1927.

Investigation showed that when food was withheld, there was a gradual fall in the level of the blood sugar. If it fell below 0.06 per cent, the usual symptoms of hypoglycemia appeared. The lowest amount of blood sugar observed was 0.04 per cent. To prevent hypoglycemia, food with the equivalent of 500 Gm. of dextrose each day was required, lunches being given between meals and three times during the night. The injection of epinephrine hydrochloride caused a rise in blood sugar, and relief of symptoms. Solution of pituitary had a similar influence, although it was less powerful. Atropine did not have any effect. A diagnosis of hyperinsulinism was made because of the resemblance of this case to case 1. The condition could not be controlled by medical measures, and since the patient was incapacitated the decision was made to resort to surgical procedures. It was hoped that a localized tumor might be found in the pancreas, the removal of which would cure the patient.

The operation was performed Sept. 12, 1928 (Judd). The pancreas and neighboring organs appeared normal. The tail of the pancreas and part of the body were resected. The portion removed weighed 14 Gm. Microscopic examination did not show visible abnormality.

After the operation, the tendency to hypoglycemia had apparently disappeared. On the second day on which no sugar or other nourishment was given, the blood sugar varied between 0.114 and 0.075 per cent. The usual postoperative feeding was commenced on the third day. Two weeks later, when food with the equivalent of 200 Gm. of dextrose was taken in twenty-four hours, the blood sugar values were subnormal, approximately 0.06 per cent, in the morning. The amount of food was, therefore, increased.

It was apparent that the tendency to hypoglycemia had not been completely abolished, but had been decidedly decreased. The patient was finally able to live on only three meals a day and without taking nourishment during the night. He returned to his home on October 25. Weekly reports show that mild hypoglycemic symptoms have occurred a few times only.

Case 3.—A man, aged 47, came to the clinic in October, 1928, because of symptoms similar to those in cases 1 and 2; they had first appeared four years before and had gradually increased in severity. Three years before admission, disturbances of sleep and somnambulism appeared; two years before, a violent convulsive attack occurred during the night. He noticed that eating relieved the symptoms or checked the attacks, so that he began to take food three times during the night as well as between meals. In spite of precautions, attacks of weakness and stupor occurred with increasing frequency, especially after exertion, and he was obliged to give up his work. About two months before admission, he was in a hospital, where food was not given after 5:30 p. m. Attacks occurred during the night, in which he became irrational and maniacal so that he was confined in a straight-jacket on several occasions. Recovery occurred spontaneously after several hours.

Examination of the blood showed that the sugar content fell when food was not taken, sometimes reaching 0.04 per cent. Hypoglycemic symptoms usually appeared when the blood sugar fell below 0.05 per cent. The ingestion of food with the equivalent of from 400 to 450 Gm. of dextrose prevented hypoglycemic symptoms when given at suitable intervals. Epinephrine and solution of pituitary showed transitory effects in checking hypoglycemia. Ephedrine also appeared to have some influence. The patient is still under observation.

COMMENT

The symptoms of hypoglycemia are remarkable in their variation, but are not difficult to recognize. The characteristic feature is the prompt relief which follows the ingestion of sugar or other carbohydrate food. Each of these patients had learned by his own experience that he could avoid or check his symptoms by eating at frequent intervals. The suggestion given by this history can readily be verified by the blood sugar test.

Although hypoglycemia can be recognized with ease, determination of the exact cause is difficult. Theoretically, the primary factors may be either failure of the liver or overfunction of the pancreas. Although the removal of the liver from an animal results in immediate fall in blood sugar, on only rare occasions has hypoglycemia been observed in cases of definite hepatic disease. These have been cases of advanced cirrhosis, acute yellow atrophy or extensive tumors of the liver. In the presence of such gross disturbances, one may feel satisfied that hypoglycemia, if present, is of hepatic origin. In most cases of spontaneous hypoglycemia, direct evidence of hepatic disorder is not manifested. Yet it is possible that the liver may still be at fault. It is conceivable that one function may fail, although other functions are intact. Unfortunately, there is no method which adequately tests the function of the liver with respect to carbohydrate metabolism.

The possibility of hyperinsulinism was first suggested by Harris,[2] who described several cases in which slight hypoglycemia and mild symptoms were present. Not until the report of our first case was a definite pathologic basis demonstrated for this previously hypothetic condition. Since then, hyperinsulinism has been recognized in two other cases of tumors of the pancreas. In one of these cases, reported by Thalhimer and Murphy,[3] necropsy revealed a nodule in the pancreas with groups of tumor cells identical in appearance with normal islands of Langerhans. In the other case, McClenahan and Norris [4] also found an adenoma of island tissue. The clinical picture of tumor of the islands of the pancreas with overproduction of insulin is now established as a disease entity as Wilder [5] has indicated.

The condition encountered in case 2 seems to indicate that hyperinsulinism may also exist without any anatomic change of the pancreas.

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2. Harris, Seale: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:729 (Sept. 6) 1924.

3. Thalhimer, W., and Murphy, F. D.: Carcinoma of the Islands of the Pancreas, Hyperinsulinism and Hypoglycemia. J. A. M. A. **91**:89 (July 14) 1928.

4. McClenahan, W. U., and Norris, W. G.: Pancreatic Adenoma with Hypoglycemia, Am. J. M. Sc., to be published.

5. Wilder, R. M.: Tumor der Langerhansschen Inseln mit Hyperinsulinismus, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40**:223, 1928.

A similar case was reported by Finney and Finney,[6] who were the first to attempt surgical treatment of this condition. Their patient had suffered from spells of mental confusion and peculiar behavior for four years, with decreases in the blood sugar to as low as 0.03 per cent. At operation the pancreas appeared normal. Following the removal of a portion weighing 22.5 Gm., the tendency of the blood sugar content to fall below normal was checked for several days. Later, hypoglycemic symptoms appeared, although apparently they were not as severe as before. In such cases, overproduction of insulin may depend on stimulation by nervous mechanism or some other cause. That the disorder may exist without visible abnormality is not surprising, since the opposite condition, diabetes, may likewise occur without visible change in the islands of Langerhans.

Direct proof that hyperinsulinism actually exists in cases 2 and 3 cannot be furnished. There is no satisfactory method of assaying the insulin in the blood. In the cases of tumors of the pancreas, the rôle of the pancreas was demonstrated positively only by surgical exploration or by necropsy, yet it is possible that the clinical differentiation of hyperinsulinism and selective hepatic insufficiency may be made by indirect methods. Epinephrine and solution of pituitary do not affect the blood sugar of a dehepatized animal. The rise in blood sugar content following the administration of these agents might, therefore, be taken as evidence that in cases 2 and 3 the hypoglycemia was not due to loss of hepatic function. In case 1, epinephrine and solution of pituitary did not have any effect, presumably because of the overwhelming amount of insulin in the body. Here the amount of sugar required to prevent hypoglycemia may help in the diagnosis. Mann and his coworkers found that a dehepatized dog requires from 0.25 to 0.5 Gm. of dextrose for each kilogram of body weight each hour to maintain the blood sugar level. The calorie equivalent of the maximal requirement is approximately equal to the basal heat production. One might assume that the loss of hepatic function in man would create a demand for a corresponding amount of sugar. Therefore, if the calorie equivalent of the sugar required to prevent hypoglycemia in a man at rest were much in excess of the basal heat production, it might indicate that sugar was required not merely to compensate for loss of hepatic function, but to meet the demand for increased utilization due to insulin. Using a rough calculation and assuming that the average basal heat production of a man is 1 calorie for each kilogram each hour, one might conclude that if more than 0.25 Gm. of sugar for each kilogram of body weight each hour

6. Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of the Pancreas, Ann. Surg. **88**:584, 1928.

were required, hypoglycemia must be due to hyperinsulinism. In case 1, approximately twice this amount was eventually needed. In cases 2 and 3, the amount of sugar needed was not great enough to make this criterion applicable. Yet in each of the three cases the diagnosis of hyperinsulinism seemed logical.

The psychiatrists who observed the case reported by Finney and Finney suspected hysteria, and the failure of the operation to give complete relief apparently led to the conclusion that "the spells are wholly psychogenic in origin." No doubt, in many such cases the patients are dismissed with this diagnosis. Other cases probably are diagnosed as epilepsy. However, when blood sugar determinations show that the symptoms are invariably associated with hypoglycemia and that immediate relief follows elevation of the blood sugar, the diagnosis of hysteria or neurasthenia is dangerous. It can be recalled that the nervous manifestations of hyperthyroidism were often attributed to neurosis.

The obvious treatment of hyperinsulinism is to provide sugar, or other carbohydrate food, in sufficient amounts and at the proper time to maintain the blood sugar level. If the symptoms are mild, this might be done without difficulty, but in the cases described, even with the knowledge of the remedy, it has been impossible for the patients to lead a normal existence. Unusual exertion or failure to take sufficient food precipitated loss of consciousness, and unbroken sleep was impossible. Medical measures have been of little value. Epinephrine hydrochloride, solution of pituitary and ephedrine have only transitory effects. Because of the analogy of the condition to hyperthyroidism, as pointed out by Wilder,[5] surgical measures appear to offer the greatest benefit. In cases of hyperinsulinism due to a localized tumor, complete cure should follow excision. Overactivity of the whole gland which probably existed in the two cases in which operations were performed is, naturally, more difficult to remedy. In neither case was complete relief obtained, but in one case the improvement was considerable.

SUMMARY

Hyperinsulinism due to overproduction of insulin from a tumor of the islands of the pancreas is now established as a disease entity. It is probable that hyperinsulinism may also be due to a functional disturbance of the pancreas. The differential diagnosis of hypoglycemia due to hyperinsulinism and hypoglycemia due to selective hepatic insufficiency is a difficult clinical problem. Two criteria may have value in differentiation: the effect of epinephrine hydrochloride and solution of pituitary, and the amount of sugar required to maintain the blood sugar level. When the hypoglycemic tendency is so strong that the patient is incapacitated, surgical treatment appears to promise relief.

Three cases are described in which there was a constant tendency to severe hypoglycemia attributed to hyperinsulinism. In case 1, there was a carcinoma of the islands of Langerhans. In case 2, surgical exploration revealed a normal appearing pancreas. Resection of a part of the pancreas was followed by considerable relief. In case 3, in which medical treatment alone was given, the patient is still under observation.

AN IMPROVED DUODENAL TUBE

ITS ADVANTAGES, WITH A BRIEF OUTLINE OF DUODENAL INTUBATION *

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Nonsurgical drainage of the gallbladder incident to a complete investigation of the gatro-intestinal tract has heretofore required several hours. With the improved tube and altered technic, it requires only one-half hour.

DESCRIPTION OF THE TUBE

The olive: The fenestrations and lumen are larger, the lumen extending throughout the entire olive; all sharp edges are rounded, polished and gold plated to prevent discoloration and corrosion.

The tube: The overall diameter of the tube and of the olive are thus approximately equal. The proximal end attachments are omitted as unnecessary. An all rubber, 3 ounce syringe with a hard rubber or bakelite cannula is all that is necessary. It facilitates the method of obtaining material for culture.

TECHNIC

The following is an outline of the technic to be used.

Time: Preferably 9 a. m., on a fasting stomach.

Material:

(*a*) Hypertonic solution of sulphate of sodium, magnesium, potassium and calcium warmed.

(*b*) Author's modified tube.

(*c*) Funnel-shaped cannula to fit the proximal end of the tube.

(*d*) Three ounce all rubber syringe.
The instruments are submerged in a jar of 95 per cent alcohol; they are thoroughly washed, but not boiled.

(*e*) Sterile water in 500 cc. flasks covered with 50 cc. jar sterilized daily.

(*f*) Sterile large test tube.

(*g*) Astringent solution.

Stage I. Position of Patient (Seated or Standing):

(*a*) Direct the olive gently to the pharynx; after one swallow the tube may be continued to notch II without any interruption or reflex gagging. Place the patient on the right side; receive the stomach contents by syphonage. Titrate and examine microscopically.

(*b*) Wash three times with 500 cc. of sterile water or with some mild astringent.

Stage II:

(*a*) Advance the tube to notch III. Allow the greater curvature of the stomach to direct the tube into the duodenum. Syphon the duodenal contents; examine microscopically and culture.

(*b*) Wash as in stomach method.

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(*c*) Localize tube.

1. Observation by injecting air: Usually sensations felt above the umbilicus indicate that the tube is in the stomach; if below the umbilicus and more definitely sensed, in the duodenum.

The sound transmission due to the pressure required with air and liquid is distinctly different, being cavernous in the stomach and muffled and distant in the duodenum.

2. Fluoroscopic localization is never needed.

Stage III:

(*a*) Instil hypertonic solution of from 25 to 50 cc. with moderate force; retain until nausea is experienced or until after a five minute lapse of time; then allow to syphon back into the sterile container. Bile fractions are obtained as usual.

(*b*) A test tube of 95 per cent alcohol is sufficient for sterilization of the proximal end of the tube, which can be placed in a sterile test tube to receive the contents for culture.

(*c*) Wash or instil suitable preferred solutions and withdraw the tube slowly without interruption.

ADVANTAGES OF IMPROVED TUBE

The advantages of the new tube are all due to its increased rigidity and diameter. Its advantages during administration are as follows:

(*a*) Swallowing, peristalsis and fluoroscopic localization are unnecessary.

(*b*) The contents of the stomach, duodenum and gallbladder can be obtained in one-half hour.

(*c*) The tube does not become knotted.

These advantages enable the operator to perform as a routine measure a technic on a par with that of the examination of the heart, lungs and kidneys.

The advantages during the instillation stage are:

(*a*) The lumen and fenestrations permit the exit of heavy mucus by syphonage alone. Essence of caroid is a distinct adjunct when tenacious mucus is encountered.

(*b*) The fanlike splashing of the duodenal wall by the hypertonic solution provides a larger surface area in stimulating the neuromuscular mechanism incident to drainage of the gallbladder.

(*c*) Reflex gagging and vomiting are practically negligible, but if they do occur, they do not eject the tube.

TOXIC ADENOMA OF THYROID*

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A review of the literature shows that toxic adenoma of the thyroid has been considered under a variety of names. Some of these synonyms are:

Enlargement of the thyroid gland in connection with enlargement or palpitation of the heart—Parry[1] (1825).

Constitutional iodism—Rilliet[2] (1859).

Iodine exophthalmic goiter; iodine Graves' disease—Trousseau[3] (1860).

Formes frustes exophthalmic goiter—Trousseau[4] (1862); Marie[5] (1883).

Secondary Basedow—Gauthier[6] (1893); Buschan[7] (1894).

Basedowified goiter—Marie[8] (1897); Struma basedowificata—Kocher[9] (1906).

Goiter heart—Kraus[10] (1898).

Iodine thyroidism—Breuer[11] (1900).

Basedowid—Stern[12] (1908-1909).

Toxic nonexophthalmic goiter—Plummer[13] (1912).

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* Submitted for publication, Dec. 28, 1928.

* From the Radium Clinic of Beth Israel Hospital, New York.

1. Parry, C. H.: Collection from the Unpublished Medical Writings **2:** 111, 1825.

2. Rilliet, F.: Mémoire sur l'iodism constitutional, etc., présenté á l'academie impériale de médecine le II Janvier 1859, Gaz. méd. de Paris, 1860, Avril.

3. Trousseau, A.: Du goitre exophthalmique, Gaz. d. hôp. **33:** 553, 1860.

4. Trousseau, A.: Du goitre exophthalmique ou maladie de Grave, Clinique, Paris **2:** 614, 1862.

5. Marie, P.: Contribution á l'étude et au diagnostic des formes frustes de la maladie de Basedow, Thèse de Paris, 1882-1883, p. 1.

6. Gauthier, G. (de Charolle): Des goitres exophthalmique, secondaires ou symptomatique, Lyon méd. **72:** 41, 82 and 120, 1893.

7. Buschan, G.: Die Basedow'sche Krankheit, eine Monographie. Von der Berliner Hufel- und -Gesellschaft preisgekrönte Arbeit, Leipsic und Vienna, Franz Deuticke, 1894.

8. Marie, P.: Maladie de Basedow et goitre Basedowifie, Bull. et mém. Soc. med. d. hôp. de Paris **14:** 57, 1897.

9. Kocher, T.: The Pathology of the Thyroid Gland, Brit. M. J. **1:** 1261, 1906.

10. Kraus, F.: Kropfherz. Krankheiten der Schilddruse, in Ebstein und Schwalbe: Handbuch der Praktischen Medizin, 1898, vol. 2, p. 240.

11. Breuer, R.: Aetiologie der Basedow'schen Krankheit und des Thyreoidismus, Wien. klin. Wchnschr. **13:** 641, 671, 1900.

12. Stern, R.: Differentialdiagnose und Verlauf des Morbus Basedowii und seiner unvolkommenen Formen, Jahrb. f. Psychiat. u. Neurol. **29:** 179, 1908-1909.

13. Plummer, H. S., in discussion following paper by Marine, D.: Anatomic and Physiologic Effects of Iodine on Thyroid Gland of Exophthalmic Goiter, J. A. M. A. **59:** 325 (Aug. 3) 1912.

Toxic adenoma of the thyroid—Plummer [14] (1913).
Adenoma with hyperthyroidism—Plummer [15] (1916).
Hyperfunctioning adenomatous goiter—Plummer [16] (1921).
Iodine hyperthyroidism—Jackson [17] (1924).
Nodular goiter with hyperthyroidism—Rienhoff [18] (1927).

In a recent study of the goiter problem, Aschoff [19] stated: "We were able to show that the nodular form was not a kind of hyperplasia or hyperplastic condition, as was then believed, but that we were dealing with a definite tumor formation, namely, adenomata." Do simple adenomas of the thyroid gland become toxic? "Indeed, they do," is Ashoff's affirmative reply. "Struma nodosa basedowificata," or toxic adenoma of the thyroid does exist. If simple nodular goiter is almost invariably synonymous with simple adenoma of the thyroid, toxic nodular goiter is equally synonymous with toxic adenoma of the thyroid. Hence, clinically, a tentative diagnosis of toxic adenoma of the thyroid is warranted whenever a nodular thyroid is associated with the constitutional symptoms of exophthalmic goiter with or without the ocular manifestations of the disease. This tentative clinical diagnosis is corroborated if iodine medication ameliorates [20] or aggravates [21] the symptoms, or if surgical enucleation or successful irradiation of the adenoma cures or markedly improves the patient.

REVIEW OF THE LITERATURE

Almost a century has elapsed since the names of Graves and Basedow have become closely associated with the clinical concept exophthalmic goiter. During this period of time, knowledge of this disease has grown and become vastly more extensive than that of its original discoverers. The so-called classic triad of symptoms—exoph-

14. Plummer, H. S.: The Clinical and Pathologic Relationship of Simple and Exophthalmic Goiter, Am. J. M. Sc. **146**: 790, 1913.

15. Plummer, H. S.: The Function of the Thyroid Gland, Normal and Abnormal, Tr. A. Am. Phys. **31**: 128, 1916.

16. Plummer, H. S.: Interrelationship of Function of the Thyroid Gland, J. A. M. A. **77**: 243 (July 23) 1921.

17. Jackson, A. S.: Iodine as a Cause of Hyperthyroidism, Lancet **44**: 324, 1924.

18. Rienhoff, W. F., Jr.: Hyperthyroidism and Its Relation to Benign Tumors of Thyroid Gland, South. M. J. **20**: 901 (Dec.) 1927.

19. Aschoff, L.: The Goiter Problem, Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924, pp. 313-339.

20. Graham, A., and Cutler, E. C.: Exophthalmic Goiter and Toxic Adenoma: Similarity of Response to Iodine, Ann. Surg. **84**: 497 (Oct.) 1926. Youmans, J. B., and Kampmeier, R. H.: Iodine in Toxic Adenoma, Arch. Int. Med. **41**: 66 (Jan.) 1928.

21. Kimball, O. P.: Differential Diagnosis of Hyperthyroidism, Ohio State M. J. **20**: 421, 1924. Boothby, W. M.: The Use of Iodine in Exophthalmic Goiter, Endocrinology **8**: 727, 1924. Jackson, A. S.: Goiter and Other Diseases of the Thyroid Gland, New York, Paul B. Hoeber, Inc., 1926.

thalmos, tachycardia and goiter—is no longer considered absolutely essential for the correct diagnosis of the disease. Formes frustes have been described and recognized. The thyroid factor is no longer considered a mere secondary phenomenon among the essential manifestations of the disease. A definite, pathologic condition of the thyroid gland has gradually become more and more recognized as the essential underlying condition and mainspring of the disease.[22] Thyrotoxicosis, hyperthyroidism and dysthyroidism have become almost universally synonymous terms with exophthalmic goiter.

Nevertheless, greater knowledge and changed conceptions of the disease have not dimmed the memory nor marred the luster of the names of Graves and Basedow. With the passing of the years their fame and popularity, instead of being on the wane, appear to be on the increase. Moreover, not only in discussions of classic exophthalmic goiter are their names frequently on the lips of every tyro in medicine, but also in association with toxic adenoma of the thyroid. And yet neither Graves [23] nor Basedow [24] ever reported any cases that could have been classed with toxic adenoma. The first observer to whom this honor is due—as was recently pointed out by Sir Humphry Rolleston [25]—is no other than Caleb Hillier Parry who "in 1786, left an account of exophthalmic goiter so complete and original that it more justly entitles him to the honor of its discovery than either Flajani (1800), Graves (1835) or Basedow (1840)." In the same study, published posthumously in 1825, to which the distinguished American medical historian, Fielding

22. Greenfield, W. E.: The Bradshaw Lecture on Some Diseases of the Thyroid Gland, Delivered Before the Royal College of Physicians, Brit. M. J. **2**:13 (Dec.) 1893. Joffroy, A., and Achard, C.: Contribution a l'anatomie pathologique de l'maladie de Basedow, Arch. de méd. expér. et d'anat. path. **5**:807, 1893. Renaut: Corps thyroide et maladie de Basedow, Semaine méd. **15**:327, 1895. Farmer, E.: Beiträge zur pathologische anatomie des Morbus basedowii mit besonderen Beruchsichtigung der Strumen, Virchows Arch. f. path. Anat. **143**:509, 1896. Muller, L. W.: Beiträge zur Histologie der normalen und der erkrankten Schilddrüse, Beitr. z. path. Anat. u. z. allg. Path. **19**:127, 1896. Hamig, G.: Untersuchungen über Morbus basedowii, Arch. f. klin. Chir. **55**:1, 1897. Hansemann, D.: Schilddrüse und thymus bei der Basedow'schen Krankheit, Berl. klin. Wchnschr. **42**:65 (Oct. 30) 1905. Ewing, J.: Exophthalmic Goiter from the Standpoint of Serum Therapy, New York M. J. **84**: 1061 and 1114, 1906. Lewis, D. D.: The Pathological Anatomy of Exophthalmic Goiter, Surg. Gynec. Obst. **3**: 476, 1906. Kocher, T.: The Pathology of the Thyroid Gland, Brit. M. J. **1**:1261, 1906. Kocher, A.: Die histologische und chemische Veränderung der Schilddrüse bei Morbus basedowii und ihre Beziehung in Funktion der Drüse, Virchows Arch. f. path. Anat. **208**:86, 1912.

23. Graves, R. J.: System of Clinical Medicine, Dublin, 1835.

24. Basedow, K.: Exophthalmos durch Hypertrophie der Zellgewebe in der Augenhohle, Wchnschr. f. d. ges. Heilk., Berlin, 1840, pp. 199-204; 220-228.

25. Rolleston, Sir Humphry: Caleb Hillier Parry, M.D., F.R.S., Ann. M. History **7**:205, 1925.

H. Garrison,[26] so eulogistically refers, there is also the first account of toxic adenoma of the thyroid reported in the medical literature.

> Miss P., of a gouty and nervous family, had had an enlargement of the thyroid for more than twenty years, which has been very much increased lately. . . . The swelling began on the right side and is now nearly equal on the left but extending far upwards. It is not sore but occasionally uneasy. . . . For the past eight or nine years, following an attack of gouty arthritis of several weeks' duration, she began to be subject to depression of spirits, frequent headaches, violent palpitation, extreme nervousness and moderate tachycardia. . . . She has taken Bark, Sponge, Calomel, Antimony, Sarsaparilla, Soda, has tried sea bathing and used mecurial friction, which made her faint. . . .

Although Parry was the original discoverer of exophthalmic goiter and toxic adenoma, he did not make any distinction between these two types of cases, for his view of the rôle of the thyroid gland in this disease—which eponymically should have been best known as Parry's disease—was far removed from the current theory of thyrotoxicosis. Instead of looking on the abnormal enlargement of the thyroid as a pathologic process responsible for the toxic clinical manifestations of the disease, he perceived in this enlargement a beneficent protective response. The physiologic function of the thyroid gland was entirely unknown during his time. Greatly impressed as he was by the enlargement of the thyroid gland, he was even more strikingly impressed by the headward throbbing carotids and the marked nervous and psychic manifestations of the disease. Hence, he concluded that the primary site and origin of the disease must be located in the brain, having been induced there by a morbid determination (flow) of blood—the current explanation for many nervous ailments during Parry's time.[27] But what puzzled Parry was that if this disease was a primary condition of the brain, what was the significance of the coincident enlargement of the thyroid gland? On further reflection and speculation, he came to the conclusion that "the coincidence is so frequent and remarkable that one can scarcely avoid suspecting that the thyroid gland, of which no use whatever has hitherto been hinted by physiologists is intended in part to serve as a diverticulum in order to avert from the brain a part of the blood, which, urged with too great force by various causes, might disorder or destroy the functions of that important organ."

If Parry assigned at least an important secondary—protective shunting—rôle to the thyroid gland in toxic adenoma, the next most important contributor to this interesting problem, Rilliet [2] of Geneva, almost entirely denied the significance of the thyroid in what has since most popularly become known as "iodine Basedow" or iodine hyperthyroidism. Under the title of "Constitutional Iodism," Rilliet,[2] in 1859, pub-

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26. Garrison, F. H.: History of Medicine, Philadelphia, W. B. Saunders Company, 1914.

27. Parry, C. H.: Elements of Pathology, London, 1815, vol. 1, p. 187.

lished a comprehensive monograph in which he exposed the dangers of the administration of iodine both in the prophylactic and in the curative treatment for simple goiter. From a study of the literature and his own observations, he collected a series of cases in which after iodine medication there developed all the typical symptoms of toxic adenoma, namely, rapid loss in weight in spite of bulimia, diarrhea, tremor, tachycardia, mental disturbances, etc. Fairly illustrative of these observations is case 1 of his own series.

RILLIET'S CASE.—A man, aged 50, had noticed since youth a hard, irregular tumor mass in the right lobe of the thyroid gland. The mass was symptomless, grew slowly and had reached the size of an orange in April, 1857, when the man accidentally first came under medical observation. Although the goiter was entirely symptomless, iodine medication was advised in order to induce the disappearance of the unsightly tumor mass. Within six days after iodine therapy was started, during which time the total dose of the drug taken barely exceeded 1 grain (0.065 Gm.) the patient developed rapid and progressive loss in weight. His eyes showed a definite stare. He became gloomy and depressed. His weakness became so profound that he was unable to attend to his occupation. There was a complete change in his personality. He became lachrymose and sleepless. His voice sounded cracked and tremulous. Both upper and lower extremities showed a definite tremor. With the progressive development of emaciation, the thyroid tumor shrank to three fourths of its former size, but the general condition of the patient had deteriorated greatly and his condition appeared to be so grave that a fatal issue was expected.

Under treatment with tonics and with a change of scene, the symptoms gradually subsided; but not before the lapse of seven months after the patient of his own accord had abruptly stopped taking the iodine and had wrathfully flung the medicine bottle with its unfinished contents into the lake of Geneva did he recover his former health.

With the complete regaining of his health and strength, the goiter returned to its original size and symptomless condition.

Of the twenty-three cases personally observed by Rilliet, twenty of the patients recovered; one had persistent symptoms at the time of the report, and two died. In addition, Rilliet found five deaths reported in the literature. In almost all these cases of so-called "constitutional iodism," with few exceptions, the toxic manifestations occurred in patients with clinically demonstrable preexisting goiter. In the majority of these cases, the goiter shrank during the height of the constitutional symptoms and returned to its former size when the patients recovered their former health. What interpretation was to be given to these important observations? What part did the goiter play in the origin and development of these toxic constitutional symptoms? Previous investigators, Roser,[28] Prevost, Lebert[29] and others, who had made similar observations, sug-

28. Roser: Ueber die sogenannte Jodkrankheit, richtiger Krankheit der vertriebenen Kropfe, Arch. f. d. ges. Physiol. **7**: 74, 1848; Ueber Jodkrankheit und über die kropfkachexie, falschlich auch Jodkrankheit genannt, ibid. **3**:494, 1859.

29. Lebert, H.: Die Krankheiten der Schilddruse, Breslau, 1862, p. 229.

gested resorption of abnormal goiter products as the underlying cause of the toxic constitutional symptoms. Rilliet considered this explanation untenable for three reasons:

1. Constitutional iodism has been observed among patients who clinically failed to show any goiter.

2. Constitutional iodism has been observed among patients in whom the thyroid swelling did not diminish at the height of the constitutional symptoms.

3. Constitutional iodism has not been observed in the great majority of patients whose goiters did disappear under treatment with iodine.

Nor did Rilliet agree with the view of the famous Parisian clinician, Trousseau, who suggested that "constitutional iodism" is merely atypical or latent exophthalmic goiter fanned into activity by iodine medication. Against this view he opposed the following differential diagnostic picture, the cardinal features of which hardly differ from those of recent publications on the differential diagnosis of toxic adenoma and exophthalmic goiter.

Constitutional Iodism	Exophthalmic Goiter
1. Fairly frequent in Geneva since the introduction of iodine therapy by Coindet[30] in 1820.	1. Not any more frequent in Geneva after than before the introduction of iodine therapy.
2. Onset after use of iodine in persons who previously were perfectly healthy.	2. Onset without the use of iodine, although intake of iodine may have aggravated the symptoms.
3. Exophthalmos is absent.	3. Exophthalmos is present.
4. Goiter is present for many months or years before the onset of the toxic constitutional symptoms.	4. Toxic constitutional symptoms are present long before the appearance of goiter.
5. Goiter is avascular, nonpulsatile.	5. Goiter is vascular, pulsatile.
6. Goiter decreases in size at the height of the toxic constitutional symptoms.	6. Goiter increases in size at the height of the toxic constitutional symptoms.
7. Goiter enlarges and returns to its former size when cachexia disappears.	7. Goiter diminishes in size when cachexia disappears.
8. Tremor is marked.	8. Tremor is faint or absent.
9. Bulimia is frequently present.	9. Bulimia is rarely present.
10. Loss in weight, in spite of bulimia, is always present.	10. Loss in weight may be absent.
11. Prognosis not very grave. The condition is only an incident in health. Remove the cause—iodine—and the patient usually gets well within a few months, without the return of the illness.	11. Prognosis grave. Cause unknown. Duration years. Relapses frequent. Mortality high.

30. Toraude, L. G.: Bernard Courtois (1777-1838) et la decouverte d l'iode (1811), Paris, Vigot Frères, 1921.

Being convinced in his own mind that "constitutional iodism" was a definite clinical entity in which neither simple nor exophthalmic goiter plays any significant part, Rilliet argumentatively queried, "Don't we admit the presence of an arsenical, lead, mercurial, or alcoholic cachexia? Why then deny to iodin a similar rôle?"

Rilliet's differential diagnostic picture failed to impress Trousseau. Prompt and incisive, Trousseau's [3] reply came back:

> When we see that such feeble doses as 10 mgm. of iodin given once in twenty-four hours are able to produce severe intoxications; when we are told by Rilliet that even a trip across the ocean in an iodin charged atmosphere is sufficient to bring in its trail all the symptoms of "Constitutional Iodism"; we are inclined to think that these exposed individuals had already been affected with exophthalmic goiter. How else can one explain this contradiction between the experience of all other observers and those of Dr. Rilliet unless we assume the prior existence of a morbid element which, under the stimulus of the iodine medication, has been aroused to markedly increased activity?
>
> Every day, in every country, in Paris as well as in Geneva, iodin is given in large doses as high as two, three, or four grams in twenty-four hours. Never have any accidents occurred, although the same dose of the medication has been kept up for several weeks. Therefore, when we see, on the contrary, that almost infinitesimal doses of iodine do at times produce . . . enlargement of the thyroid gland, bulimia, and various nervous manifestations, we must admit that in these exceptional instances we are dealing with cases of exophthalmic goiter.

In his reply, Trousseau [4] paid no attention to the presence or absence of exophthalmos as an important differential diagnostic point between "constitutional iodism" and exophthalmic goiter. For, in common with Parry and other observers, he had known of cases of exophthalmic goiter without exophthalmos. Indeed, so well informed was he on the variations of the clinical course of the disease that he discussed freely and deliberately formes frustes cases of exophthalmic goiter long before Pierre Marie, in 1883, wrote his famous thesis in which he called special attention to these atypical forms, in which at times neither clinically demonstrable goiter nor exophthalmos is present.

Although the subject of toxic adenoma had been thus unknowingly receiving considerable attention in the medical literature,[31] it did not loom large either as a theoretical or a practical problem until after the thyroid factor assumed the center of the stage in 1886, when Moebius [32] first formulated the thyrotoxic theory of exophthalmic goiter. When the inhibitions erected universally by the adherents of the neurogenic theory against incriminating the thyroid gland as the underlying cause of the toxic manifestations in exophthalmic goiter had been sprung by

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31. Sattler, H.: Die Basedow'sche Krankheit **2**: 537, 1910.

32. Moebius, P. J.: Vom Verhaltnisse der Polioencephalitis zur Basedow'schen Krankheit, in Jendressik, E.: Schmidt's Jahrbücher der Medizin, 1886, vol. 210, p. 237.

Moebius' keen reasoning,[33] surgery at once boldly entered the therapeutic field. Thyroidectomy for the curative treatment of exophthalmic goiter suddenly received a tremendous impetus. Whereas until 1886, scarcely a dozen reports of surgical intervention in cases of exophthalmic goiter are contained among the 375 references quoted by Halstead [34] in his monograph on "The Operative Story of Goiter," within the next decade more than 100 reports are tabulated by Sattler [35] and Kinnicutt.[36]

It was soon perceived by every careful student of patients on whom thyroidectomy had been performed that the surgical results were strikingly different in cases of "primary" from those in "secondary" cases of exophthalmic goiter, in which the symptoms had supervened on an old preexisting goiter. Whereas in "primary" exophthalmic goiter the surgical failures were many and the recurrences frequent, the success after the initial mortality in cases of "secondary" or "goiter heart" was satisfactory. So strikingly different were these results that such eminent students of the disease as Gauthier,[6] Buschan,[7] Marie,[8] Kraus [10] and others who continued to cling to the nervous system as the primary site and origin of the disease, and assigned to the thyroid a mere secondary rôle in primary exophthalmic goiter, acceded to the thyroid a primary thyrotoxic rôle in secondary Basedow.

Briefly summarized, the chief arguments of these eminent clinicians in favor of the dual nature and origin of toxic goiter were as follows:

Exophthalmic Goiter	Secondary Exophthalmic Goiter, "Goiter Heart" (Toxic Adenoma)
1. Occurs in younger persons.	1. Occurs in elderly persons.
2. Goiter develops long after the onset of the toxic constitutional symptoms.	2. Goiter exists for many years before the onset of the toxic symptoms.
3. Exophthalmos is frequently present.	3. Exophthalmos is frequently absent.
4. The course of the disease is frequently severe.	4. The course of the disease is often mild.
5. Surgical intervention is rarely curative.	5. Surgical intervention is frequently curative.

The major objection, however, which was specially stressed by Kraus,[10] in 1898, against the unitary conception of exophthalmic goiter and "goiter heart" and against the thyrotoxic origin of primary exoph-

33. Moebius, P. J.: Ueber des Wesen der Basedow'schen Krankheit, Centralbl. f. Nerven. u. Psychiat. **10:** 225, 1887.

34. Halstead, W. S.: The Operative Story of Goiter, Reprint, Bull. Johns Hopkins Hosp. **19:** 71, 1920.

35. Sattler, H.: Die Basedowsche Krankheit, vol. 1, Leipzig, 1909.

36. Kinnicutt, F. P.: The Theory of the Thyroid Origin of Graves' Disease with its Bearing on the Surgical Treatment of the Disease, M. Rec. **49:** 541 (April) 1896.

thalmic goiter, was the failure, by means of thyroid products, to produce experimentally exophthalmos and the other ocular signs in the presence of all the other toxic phenomena of the disease.

Hardly had this chief objection been formulated by Kraus, when it was promptly answered by a series of fortuitous human clinical experiments reported by Notthaft,[37] Gauthier [38] and Breuer.[11]

NOTTHAFT'S CASE.—A man, aged 43, slightly distressed by obesity, was advised by a friendly druggist to try 5 gr. (0.324 Gm.) tablets of thyroid extract to produce a reduction cure. Within five weeks the patient consumed 1,000 such tablets. The result was a rapid loss of 30 pounds (13.6 Kg.) in weight, accompanied by the development of all the symptoms of exophthalmic goiter, including exophthalmos. The medication was stopped at the beginning of the sixth week. Six months later the constitutional symptoms were diminished, but exophthalmos was still present. It was four months later before the patient fully recovered.

Even more illuminating was Gauthier's case.

GAUTHIER'S CASE.—A woman, aged 50, had a slowly growing goiter of several years' duration. The tumor mass, more marked on the left, had reached the size of an orange. Presently, she began to suffer from dyspnea and orthopnea. She applied to a druggist who gave her an iodine preparation to be painted over the region of the neck and tumor. A few weeks later, failing to note any improvement, she again consulted the same druggist who prescribed, in addition, iodine medication internally. The result was the development a few days later of typical exophthalmic goiter with marked exophthalmos. She was treated medically, and four weeks later she began to show signs of improvement. Two or three months later, thyroidectomy was performed. Twenty-four hours after the operation, the patient died in a typical thyroid crisis. Necropsy failed to show any organic disease to account for this sudden death.

Equally illuminating and corroborative of these facts, showing the hidden relationship between "simple" and toxic goiter and the close relationship between toxic adenoma and exophthalmic goiter, were the observations of Breuer in nine cases of goiter, of which the following three are excellent illustrations:

BREUER'S CASE 1.—A woman, aged 56, first came under observation on March 13, 1900, complaining of slight palpitation on exertion, slight headache and drawing pains in her legs.

Her past history was entirely negative except for a goiter which had first been noticed eighteen years prior to observation, during pregnancy. The goiter, after growing rapidly in size for several weeks, had remained stationary ever since. The only two abnormal objective signs found on examination were: a large, soft goiter; a soft diastolic murmur over the sternum. The patient looked calm and

37. Notthaft, A.: Ein Fall von artificiellen akuten thyreogenen Morbus basedowii, Zentralbl. f. inn. Med. **19:** 353, 1898.

38. Gauthier, L.: Encore l'iode et la glande thyroide, Rev. méd. de la Suisse Rom. **19:** 618, 1899.

well nourished. She had no tremor, and her pulse was not accelerated. A diagnosis of arteriosclerosis was made, and iodine medication was prescribed. For two weeks, with an interruption of nine days between, she took a daily dose of 0.9 Gm. Within less than a week after the medication was started the patient developed rapid reduction in the size of the goiter, marked restlessness, tremor, flashes of heat, rapid loss in weight in spite of good appetite and twenty diarrheal stools daily. The frequency of the pulse rate rose to 120. The thyroid gland was found to have shrunken considerably in size, and on palpation, a node, the size of a hazel-nut, was felt in the left lobe of the gland. Exophthalmos and von Graefe's sign were absent, but a slight stare and Stellwag's sign were detected. The symptoms continued for several weeks after the medication was discontinued, and when the patient was last examined her pulse rate was still 100.

Case 3.—A woman, aged 58, had an old goiter which had never caused any Basedow symptoms. Within one week after taking 10 Gm. of potassium iodide for arthritic pains, she developed headaches and marked weakness. She stopped the medication, but the weakness kept increasing. The goiter had shrunk only slightly, but the patient became irritable and developed marked tremor and tachycardia. There was rapid wasting, especially of the breasts. Diarrheal stools were frequent but painless. On examination, exophthalmos was absent but all the other ocular signs of exophthalmic goiter were present, namely, stare and Dalrymple, Stellwag and von Graefe's signs. Her pulse rate was 100. Slow improvement was first noticed one month after the iodine medication was discontinued.

Case 6.—A woman, aged 30, had a "thick neck" since youth. She had always been well, had never been nervous or shown symptoms of exophthalmic goiter. Her weight before the onset of her present illness was 130 pounds (59 Kg.). Purely for cosmetic reasons, she wished to reduce the size of her thick neck, which measured 38 cm. in circumference. At the advice of a physician she took thyroidin tablets for four weeks, but failed to notice any reduction. She was then given an ointment of iodine-potassium-iodide to rub into the neck daily. This treatment was carried out for a period of forty-four days. The goiter began to shrink in size, but simultaneously with this shrinkage the patient began to lose weight rapidly. She grew nervous and developed palpitation even at rest. She stopped the medication, but her symptoms persisted. Her skin felt hot. She grew weak, and was annoyed by polyuria. She perspired excessively and suffered from bulimia. Twenty days after the iodine medication was discontinued, examination showed a parenchymatous goiter with two small nodular masses in the left lobe of the gland. In addition to tremor and tachycardia, definite bilateral exophthalmos and positive Stellwag and von Graefe's signs were present.

From a study of these three cases and similar ones, Breuer came to the conclusion that all the toxic phenomena in "iodin-thyroidism" as well as in typical exophthalmic goiter are due to resorption of thyroid products. He explained the absence of eye phenomena in some cases and their presence in others on the basis of special local vasomotor and ocular resistance or susceptibility, just as Kraus has assumed that in "goiter heart" there is a special cardiovascular vulnerability to the action of the resorbed thyroid products. Viewed by the light of these observations, Breuer felt that the unitary conception of exophthalmic goiter was thus vindicated and Kraus' objections fully answered.

This unitary conception of toxic goiter originally formulated by Moebius [39] had been repeatedly stressed by its author in numerous publications. As late as 1906, after a score of years of intensive study and investigation of this important problem, Moebius [39] failed to perceive any fundamental distinction between the various types of toxic goiter. He maintained:

> The symptoms in secondary Basedow present the same characteristics as in the primary form. The cardiac disturbances, exophthalmos, and mental changes occur equally in both. It matters little whether the goiter preceded the symptoms by one year or fifteen years. . . . It is incorrect to speak of complete and incomplete Basedow. . . We should rather classify our cases into mild and severe forms, into those presenting many or few symptoms.

These views so tersely and emphatically expressed by Moebius kept gaining ever wider recognition among clinicians and pathologists toward the end of the first decade of the twentieth century. As late as June, 1909, L. B. Wilson,[40] the director of the pathologic department of the Mayo Clinic, emphatically declared:

> In examining cases of so-called simple goiter for exophthalmic symptoms we must get completely away from our old teachings that exophthalmos is a sine que non of Graves' disease. The disturbed nervous, metabolic and muscular phenomena are quite essentially diagnostic. Looked at from the clinical standpoint then, a case of Graves' disease is one with an enlarged thyroid and exhibiting symptoms of too much thyroid secretion, while a case of simple goiter is one with an enlarged thyroid, but exhibiting no such symptoms.

Even more emphatic at this time in his unitary attitude toward toxic goiter was Charles H. Mayo.[41] In discussing the operative treatment of "hyperthyroidism," he stated:

> The name commonly used exophthalmic goiter, is not a good term as many of the patients do not have a goiter and others do not have a prominent eye, while some of them have neither of these symptoms in the early stages of the disease when a diagnosis might be made if these symptoms were not considered of so much importance. . . . In a death from an unoperated acute Graves' disease in which the thyroid was apparently normal to palpation both before and after death, the autopsy showed the gland to weigh nearly three times the normal, and to be typical in the structural changes present.

However, while this unitary conception of toxic or exophthalmic goiter was being publicly championed in print by Wilson and Mayo, an undercurrent of doubt was gradually emerging and sweeping aside the

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39. Moebius, P. J.: Die Basedowsche Krankheit, Wien, 1906.

40. Wilson, L. B.: The Pathological Relationship of Exophthalmic Goiter and Simple Goiter, Surg. Gynec. Obst. **8**: 588, 1909.

41. Mayo, C. H.: The Operative Treatment of Hyperthyroidism, Surg. Gynec. Obst. **8**: 602, 1909.

former unified point of view among the members of the Rochester Clinic. The first to recede from his former unitary view was the pathologist, Wilson.[42] Only four years later, in 1913, he declared:

> The solution of problems of the pathology of the thyroid has long been rendered more difficult by indefinite clinical diagnoses and nomenclature. . . . While non-toxic cases usually have been diagnosticated, "Simple goiter," yet many cases with mild symptoms have also been called "simple goiter," and many cases, though not true exophthalmic yet markedly toxic, have been called by most clinicians "exophthalmic goiter." . . . Though a sharp distinction between the two clinical types of toxic cases—exophthalmic and non-exophthalmic—had not been made in 1908, I was able to show that pathologically there were two distinct types of glands to be found among thyroids removed from toxic goiter cases. . . . Hypertrophies, hyperplasias, and extreme regenerations, constituted 79 per cent of the total number of specimens examined, while . . . fetal and colloid adenomas, the adenomatoses and the so-called simple thyroids, constituted 21 per cent of the specimens examined. . . . In reviewing the clinical data of his more recent cases, Plummer has found that practically all, if not all, of the cases of true exophthalmic goiter lie in the pathological groups showing hypertrophy and hyperplasia, while the toxic non-exophthalmic cases are scattered among the other pathological groups.

Even more emphatic of the dual character of toxic goiter is Plummer's [13] own original contribution which appeared simultaneously with Wilson's. He declared:

> Exophthalmic goiter is a definite clinical complex always associated with hyperplasia of the thyroid, and . . . should be sharply distinguished from the constitutional state or states that may develop with non-hyperplastic goiter. . . . Can we associate the symptom-complex of non-hyperplastic toxic goiter with any definite pathological change in the thyroid? For the present this question must be answered in the negative.

This negative answer, however, is not entirely consistent with an important positive statement made incidentally in the text. Although the close identification of toxic nonhyperplastic goiter with toxic or "hyperfunctioning" thyroid adenoma had not as yet been definitely formulated in Plummer's mind, nevertheless the budding growth of this hypothesis can be perceived clearly emerging through the lines. In referring to the thyrogenic origin of exophthalmic goiter, he stated:

> While I do not wish to enter into a discussion of this subject at the present time, I wish to call attention to a point in support of this theory that, as far as I know, has not hitherto been made, namely that an individual, 22 years, with an adenoma of the thyroid has a definite chance of developing a train of symptoms during the thirty-sixth year so similar to the symptom-complex associated with hyperplastic thyroid that the best-trained diagnosticians are constantly confusing the two conditions.

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42. Wilson, L. B.: The Pathology of the Thyroid Gland in Exophthalmic Goiter, Am. J. M. Sc. **146**: 781, 1913.

Precisely how definite this chance is when judged by the frequency of association of adenomas with toxic nonexophthalmic goiter at the time of operation at the Mayo Clinic was discussed by Wilson the following year in two contributions.[43] In a study of the pathology of 374 thyroids from toxic nonexophthalmic goiter,[44] the following distribution of the adenomas was found:

1. In 155 cases, "clinically in Plummer's sub-group I, i. e., cases in which the clinical picture closely resembles and, in many instances, cannot be differentiated from, the cardiovascular complex resulting from alcoholic, syphilitic, septic, and other well-known toxins," early fetal adenomas constituted 7 per cent; degenerating fetal adenomas, 14 per cent; adult "colloid" adenomas, 21 per cent; secondary regeneration of atrophic parenchyma of "colloid" goiter, 17 per cent; atrophic parenchyma, "colloid" thyroids, adenomatoses, etc., 2 per cent.

2. In 129 "cases with symptoms closely approaching the picture of Graves' disease," early fetal adenomas constituted 12 per cent; degenerating fetal adenomas, 33 per cent; adult "colloid" adenomas, 3 per cent; secondary regeneration of atrophic parenchyma of "colloid" goiter, 50 per cent; atrophic parenchyma, "colloid" thyroids adenomatoses, etc., 2 per cent.

3. In ninety cases with mild or doubtful toxic symptoms of exophthalmic goiter, early fetal adenomas represented 10 per cent; degenerating fetal adenomas, 18 per cent; adult "colloid" adenomas, 19 per cent; secondary regeneration of atrophic parenchyma of "colloid" goiter, 9 per cent; atrophic parenchyma, "colloid" thyroids, "adenomatoses," etc., 44 per cent.

An association of from 42 to 44 per cent of adenomas with toxic nonexophthalmic goiter is sufficiently interesting and instructive to invite investigation into its significance. But of what proof is this association per se that the adenomas stand in any etiologic relationship to the development of thyrotoxic symptoms? Did not Wilson's further studies[45] record the fact that in a series of 2,356 thyroids from patients on the "simple goiter" list 45 per cent—the same proportion as in the toxic group—were composed principally of encapsulated adenomas, while the 17 per cent of patients on this list who presented toxic symptoms had thyroids showing histologically "secondary regenerations" and no adenomas? Were there any specific microscopic changes in the adenomas

43. Wilson, L. B.: A Study of the Pathology of the Thyroids from Cases of Toxic Nonexophthalmic Goiter, Am. J. M. Sc. **147:** 344, 1914; Relation of the Pathology and the Clinical Symptoms of Simple and Exophthalmic Goiter, J. A. M. A. **62:** 111 (Jan. 10) 1914.

44. Wilson (footnote 43, first reference).

45. Wilson (footnote 43, second reference).

of the clinically toxic group which were not present in the adenomas of the atoxic group? If, as stated by Wilson, the same microscopic changes were found in both groups of cases, what were the reasons that prompted Plummer to embrace the assumption of toxic adenoma or hyperfunctioning thyroid adenoma?

Apparently the chief, if not the only, reason at this time that induced Plummer to embrace the hypothesis of toxic adenoma was the important clinical observation that in "adenoma with hyperthyroidism" the toxic phenomena disappear within a few weeks after the enucleation of the adenoma—in other words, the same clinical observations which long ago had made Gauthier,[6] Buschan,[7] Marie,[8] Kraus [10] and others formulate their dual theory of toxic goiter.

The stimulus derived from this clinical observation alone, the constancy of which, according to Plummer, remains unchanged at the Mayo Clinic until recent date, would have sufficed to render strong support to the clinical assumption of toxic nodular goiter or toxic adenoma of the thyroid. Suddenly and unexpectedly, laboratory research set free an agent that was destined to exert a powerful stimulus to convert this assumption of toxic adenoma or hyperfunctioning thyroid adenoma into a firm, well grounded scientific hypothesis. This released agent, the most active constituent of the thyroid gland, was the newly discovered chemical decomposition product—thyroxin.[46]

In 1914, Kendall separated from the thyroid gland by means of alkaline alcoholic hydrolysis two groups of iodine compound: group A, insoluble in acids; and group B, acid soluble. By further hydrolysis of the A group, the compound containing iodine was separated in pure crystalline form, while no definite substance was isolated from the B group. Although the total iodine of the gland was found equally divided between the two groups, their physiologic and pharmacologic activity was strikingly unequal and dissimilar.

> In testing B for physiologic activity, it was found that no apparent effects are produced when B is given experimentally to a normal animal or human being, but that a considerable degree of activity is manifest when B is given to patients suffering from cretinism, myxoedema and certain conditions of the skin. . . . No toxic effects have been produced by the administration of B even in large amounts. . . . In strong contrast to this nontoxic effect of B is the action of A. . . . It was found that the typical effects of adminstration of desiccated thyroid—rapid increase in pulse rate and vigor, increase in metabolism with loss in weight, and increase of nervous irritability—are all produced by the A constituents . . . through all the various stages of purity, up to and including the crystalline compound containing 60 per cent of iodin. . . . Although both

46. Kendall, E. C.: The Isolation in Crystalline Form of the Compound Containing Iodine, Which Occurs in the Thyroid: Its Clinical Nature and Physiologic Activity, J. A. M. A. **64**:2042 (June 19) 1915; Experimental Hyperthyroidism, ibid. **69**: 612 (Aug. 25) 1917.

A and B contain iodin . . . the toxicity of A is in direct proportion to its iodin content, but B iodin given in equal amount produces no apparent effect. . . . The actual amount of the crystalline iodin compound necessary to produce marked effect is exceedingly small. A total of 11 mg. (one-sixth grain), given in divided doses during a period of fourteen days to a cretin weighing forty pounds, increased the pulse rate from 90 to 140. A total of 30 mg. (one-half grain), given in divided doses over a period of eighteen days to a woman weighing 112 pounds, increased the pulse rate from 75 to 130.

Further observations by Plummer [16] showed that in a normal person "2 mg. of thyroxin a day may hold the basal metabolism 20 to 30 per cent above normal, 3 mg. a day may hold the basal metabolism 50 per cent above normal."

These chemical and physiologic discoveries led Plummer to formulate the following deductions:

1. Hyperthyroidism is the physiologic state of an individual otherwise normal when the thyroxin in the tissues is sufficient to hold the basal metabolism above normal.

2. Hypothyroidism is the opposite of hyperthyroidism.

3. All the phenomena of pure hyperthyroidism are those that must attend a sustained elevation of the basal metabolism.

4. The status of hyperfunctioning adenomatous goiter is the result of a pure hyperthyroidism. . . . The assumption that the status of adenomatous goiter is attributable simply to an excess of the normal thyroid product (pure hyperthyroidism) rests largely on a correlation of at least approximately accurate observations.

They are:

The physiologic status of a thyroidless individual returns to normal when the basal metabolism is brought to normal by the administration of thyroxin.

The phenomena induced by the administration of thyroxin and the phenomena associated with adenomatous goiter are identical and are those that must attend a sustained elevation of the basal metabolism.

These phenomena disappear with the dropping of the basal metabolism to normal within three weeks after the enucleation of the adenoma.

The status of exophthalmic goiter, while in the main hyperthyroid, cannot be attributed wholly to an excess of the normal thyroid product. The characteristics of exophthalmic goiter may be due to an incomplete thyroxin molecule.

If, in addition to these differential features, is added Plummer's further statement [47] that iodine is either ineffectual or harmful in the management of toxic adenoma and is of marked temporary benefit in the treatment for exophthalmic goiter, then all the basic reasons on which the concept of toxic adenoma of the thyroid was built up have been enumerated.

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47. Plummer, H. S.: The Thyroid Gland, St. Louis, C. V. Mosby Company, 1926.

How was this concept of toxic adenoma of the thyroid received in the scientific medical world?

The answer to this question can best be found from a consideration of the response of the pathologists, the surgeons, the internists, roentgen therapists and the radium therapists.

The Response of the Pathologists.—With the single exception of the pathologists [48] of the Mayo Clinic, where this hypothesis originated, few pathologists of note on the American continent embraced this clinical-pathologic concept of toxic adenoma. In the latest editions of such standard textbooks on pathology as those of MacCallum [49] and Delafield, Prudden and Wood [50] not a single word is mentioned about toxic adenoma. "I have observed Graves' symptoms with a fetal adenoma of the thyroid during a period in which the thyroid tumor was invaded by mammary carcinoma," is all Ewing [51] had to say about toxic adenoma of the thyroid. Karsner,[52] who devoted a few paragraphs to this problem, stated that the proofs submitted thus far are inadequate to establish the authenticity of toxic adenoma as a clinical-pathologic entity. Stengel and Fox [53] were noncommittal on the subject. They shifted both the concept and the burden of proof on the shoulders of the clinician. In discussing the pathologic anatomy of the thyroid gland in exophthalmic goiter and toxic adenoma, they declared:

> Adenomatoid goiter of papillomatous type . . . is . . . usually believed by clinicians to be present in exophthalmic goiter. . . . These forms are general, but in certain instances the hyperplasia tends to remain in isolated areas or nodules. . . . Such cases may give toxic symptoms and are designated "toxic adenomata" by clinicians. Such areas are usually multiple.

In contrast to the negative or noncommittal attitude of the great majority of American pathologists is the ready acceptance of this hypothesis by a number of their eminent European colleagues.[54] In a recent discussion of the goiter problem, Aschoff stated:

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48. Wilson, L. B.: The Pathology of Nodular (Adenomatous?) Goiters in Patients With and Those Without Symptoms of Hyperthyroidism, Am. J. M. Sc. **165**: 738, 1923.

49. MacCallum, W. G.: Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1925.

50. Delafield, F., and Prudden, T. M.: Text-book of Pathology, revised by Wood, 1927.

51. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922, p. 898.

52. Karnser, H. T.: Human Pathology, Philadelphia, J. B. Lippincott Company, 1926, p. 843.

53. Stengel, A., and Fox, H.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1927.

54. Aschoff (footnote 19). Muir, R.: Textbook of Pathology, Philadelphia, J. B. Lippincott Company, 1924. Wegelin, C., in Hende, E., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 1, p. 228.

We were able to show that the nodular form was not a kind of hyperplasia . . . but . . . a definite tumor formation, namely adenomata. . . . I lay great stress upon the distinction between simple hyperplasia and tumor formation. . . . With a real tumor formation there may be hyperfunction, or dysfunction, or hypofunction. . . . With you [Americans] only the Basedow gland and the toxic adenoma, which correspond with our nodular proliferating and parenchymatous colloid goiters, are concerned in hyperthyroidism. We deliberately also include the diffuse colloid goiter, but only the proliferating form of it.

Running in a similar vein are the views of Carl Wegelin, the successor of Langhans at the university of Bern, the most famous city in Switzerland for the study of goiter pathology during the past two hundred years.

The Response of the Surgeons.—Numerous, although not entirely unanimous, are the members of the surgical specialty who embraced Plummer's hypothesis of the dual nature of thyrotoxicosis.[55] While the overwhelming majority of surgeons throughout the world unequivocally subscribed to Plummer's views on toxic adenoma as a clinical entity distinct from exophthalmic goiter, a number of prominent surgeons who perform operations on the thyroid are definitely opposed to this dual concept.

Crotti [56] stated:

So far as exophthalmos is concerned, any one, I am sure, has observed severe cases of primary thyrotoxic goiter or the "exophthalmic goiter" of Plummer, without any ocular symptoms whatever. . . On the other hand, in secondary thyrotoxic goiter, or "adenoma with hyperthyroidism" of Plummer, more than once the ocular symptoms have been very marked, exophthalmos included. . . . So far as the other symptoms are concerned . . . although again usually not so intense or so frequent as in the primary form of thyrotoxicosis . . . they are so frequently enough present to preclude a fundamental clinical distinction. . . . The surgical results obtained speak also against any fundamental clinical difference of these two conditions.

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55. Mayo, C. H.: Adenoma with Hyperthyroidism, Ann. Surg. **72**:134 (Aug.) 1920. Frazer, C. H.: The Management of Toxic Goiter from the Surgical Point of View, Ann. Surg. **72**: 155 (Aug.) 1920. De Courcy, J. L.: Results Following Two Hundred and Forty-Five Thyroidectomies, Am. J. Surg. **35**:342 (Nov.) 1921. Haggard, W. D., and Dunkley, F. D.: Thyrotoxic Adenoma, with Remarks on Basal Metabolism in Diagnosis of Goiter, Surg. Gynec. Obst. **35**:553, 1922. Jackson, A. S.: Iodin Hyperthyroidism, Am. J. M. Sc. **170**:271, 1925. Chapman, T. L.: Lowering of Mortality in Treatment of Toxic Adenoma of the Thyroid, Minnesota Med. **8**:653, 1925. Hoalst, J.: Weitere Beiträge zur Pathologie und Therapie der toxischen Stumen, Acta. chir. Scandinav. **61**:385, 1927. Abell, I.: Multiple Adenomata of the Thyroid, S. Clin. N. Amer. **2**:1325, 1922.

56. Crotti, A.: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1922, p. 351.

Hertzler [57] declared:

> It is a mistake to do a mere enucleation in toxic adenoma . . . the whole gland of toxic adenoma is diseased. The histology indicates that it is injured beyond repair. According to present methods we remove a part of the diseased tissue. This is unsurgical. The demands of ideal surgery dictate that the whole of the diseased tissue shall be removed. The question is, are we able at this time to meet the ideals in the surgical treatment? The result is myxoedema. This myxoedema can be controlled by the use of thyroid extract. There are no more comfortable persons than these myxoedemics who take their grain a day.

Whether any one will accept Hertzler's impressions as a correct characterization of "these myxoedemics" or doubt the value of the price paid, his failure to relieve the symptoms in toxic adenoma by mere enucleation is sufficiently illuminating to deserve emphasis.

Speaking from a vast experience, second only to that of the Mayo Clinic, the astute clinician and brilliant surgeon [58] of the famous Cleveland Clinic declared: "Clinical evidence of the functional activity of adenomata is found in the frequent development of symptoms identical with those which are characteristic of exophthalmic goiter and in the disappearance of those symptoms after the removal of the adenoma." Having made this admission of the existence of a clinical group of cases of toxic goiter to which the term toxic adenoma is applicable, Crile does not fail to make it clear that he does not perceive a fundamental distinction between toxic adenoma and exophthalmic goiter. The former he considers only a phase or a stage in the development of the latter. Hence, he continued, "it would seem as if adenoma caused. . . . every grade of toxemia, progressing from myocarditis, increased blood presure, nervousness, and increased basal metabolism to true exophthalmic goiter." In discussing operative technic, he disclosed the fact that the surgical problem in toxic adenoma of the thyroid is not always that of a simple and safe enucleation. . . . "In extremely grave cases it may be necessary to diminish the thyroid activity by multiple steps; ligation of one vessel; ligation of the second vessel; partial lobectomy; complete lobectomy; when necessary allowing intervals of a month or more between any two of these stages."

One of the most recent and formidable combatants against the dual theory of thyrotoxicosis and against toxic adenoma, either as a clinical or as a pathologic entity, is Rienhoff [59] of Johns Hopkins Hospital. From a study of 1,019 cases of toxic goiter at that institution during the past

57. Hertzler, A. E.: The Development and Nature of the So-Called Toxic Adenomas, Endocrinology **10:** 175, 1926.

58. Crile, G. W.: Toxic Adenoma in Relation to Exophthalmic Goiter, Ann. Surg. **72:** 141, 1920.

59. Reinhoff, W. F., Jr.: Hyperthyroidism and its Relation to Benign Tumors of Thyroid Gland, South. M. J. **20:** 901, 1927.

quarter of a century, Rienhoff came to the conclusion that, pathologically, thyroid hypertrophy and hyperplasia is the underlying cause of the disturbance in both cases of exophthalmic goiter and cases of nodular goiter with hyperthyroidism (toxic adenoma). Neither in their clinical course, response to iodine, or surgical results, did toxic adenoma at Johns Hopkins differ from classic exophthalmic goiter except as the variation of a single disease, which in different persons may run different grades of severity. Rienhoff's objections to the dualistic theory of toxic goiter are deeper and more fundamental than those of the other dissenting surgeons. He maintains—and is sustained by one of the oldest students of the pathology of exophthalmic goiter in America, Dean Lewis [60]—that the pathologic histology in toxic adenoma does not differ in its essential characteristics from that of exophthalmic goiter. The only difference is that of extent and of degree of involvement of the gland. Whereas in the typical severe cases of exophthalmic goiter at the height of the clinically toxic stage of the disease, microscopic studies usually reveal diffuse hypertrophy and hyperplasia; in the milder forms of exophthalmic goiter or in toxic adenoma a localized or patchy hypertrophy and hyperplasia is found. Clinically, these patchy areas of hypertrophy and hyperplasia are felt as nodules in the thyroid, and are most frequently the cause of toxic nodular goiter. It is these localized patches of hypertrophy and hyperplasia, frequently surrounded by areas of fibrosis, which have been erroneously interpreted by pathologists as true neoplastic formations, namely, adenomas. True neoplasms, true adenomas, Rienhoff contended, do occur but have been found in only 8 per cent of the cases of nodular goiter with hyperthyroidism at the Johns Hopkins Hospital.

Moreover, with his studies and observations as a basis, Rienhoff expressed the belief that in toxic nodular goiter a state of diffuse hypertrophy and hyperplasia precedes the development of the nodular areas. These localized nodular enlargements occur when, due to either iodine medication or spontaneous regression, discrete areas of the affected gland fail to involute or undergo hyperinvolution. When an exacerbation of the disease occurs, the morbid process may manifest itself either in the localized areas or in the nodules, leaving the surrounding parenchyma unaffected; or, which is more frequently the case, the nodular masses become the seat of pathologic activity while the intervening tissues remain normal. In either case one is not dealing with a single toxic nodular area or toxic adenoma but most frequently with multiple toxic adenomas or diffuse hyperplasia of the entire gland. Hence, as far as the surgical therapeutic indications are concerned, Rienhoff came to

60. Rienhoff, W. J., Jr., and Lewis, D. D.: Relation of Hyperthyroidism to Benign Tumors of the Thyroid Gland, Arch. Surg. **16:** 79 (Jan.) 1928.

the same conclusion as Crotti, Hertzler and Crile that the best results are obtained by a subtotal thyroidectomy and not by a mere enucleation.

Are these observations that toxic adenoma usually spells toxic adenomas merely confined to the experience of the previously mentioned surgeons? Are only Goetsch,[61] Lahey,[62] Else,[63] Terry [64] and others the only ones who find that in toxic adenoma as in exophthalmic goiter successful surgical intervention necessitates subtotal thyroidectomy? Does the experience of the surgeons at the Mayo Clinic who perform operations on the thyroid completely corroborate Plummer's contention that a mere enucleation of the adenoma cures the patient of his toxic symptoms in three weeks? Let one consult Judd [65] from the Mayo Clinic, whose surgical late-results in toxic adenoma are open for inspection.

In a series of 100 cases of toxic adenoma of the thyroid in which operation had been performed Judd reported the presence of the adenomas as follows: right and left lobes involved, forty-nine cases; right lobe, isthmus and left lobe, fourteen cases; right lobe and isthmus, four cases. In only 33 per cent of the cases was the adenomatous process on gross clinical examination limited to the isthmus or one lobe. Did Judd obtain the best results with a mere enucleation? Does he recommend enucleation as the method of choice in operating for toxic adenoma? Apparently not, for he stated that "in most cases the best operative results are obtained by subtotal thyroidectomy, which is accomplished by removing all except the posterior part of each lobe. The immediate benefit derived from the operation is greater than if lobectomy is done." Did all the patients with toxic adenoma of the thyroid who were operated on by such an eminently experienced surgeon like Judd recover in three weeks, as claimed by Plummer repeatedly in his various publications? Decidedly not. A careful review of the results at the end of two years postoperatively shows that nine patients died from all causes; two were not benefited; six showed the presence of tremor; eleven, change of voice; seventeen, loss of strength; twenty-three, tachycardia; twenty-eight, dyspnea; twenty-nine, palpitation, and forty-five, nervousness.

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61. Goetsch, E.: The Pathology, Diagnosis and Surgical Treatment of Goiter, Northwest Med. **21**: 97, 1922.

62. Lahey, F. H.: The Treatment of Adenomata of the Thyroid, S. Clin. N. Amer. **4**: 1395, 1924.

63. Else, J. E.: Adenomatosis or Diffuse Adenomatous Goiter, J. A. M. A. **85**: 1878 (Dec. 12) 1925.

64. Terry, W. E.: Surgical Considerations of Goiter, Northwest Med. **21**: 324, 1922.

65. Judd, E. S.: Results of Operation for Adenoma with Hyperthyroidism and Exophthalmic Goiter, Ann. Surg. **72**: 145 (Aug.) 1920.

If the observations of these eminent surgeons are correct, what remains then of the dual structure erected by Plummer to distinguish toxic adenoma from exophthalmic goiter? Is it the difference in response to iodine? But have not Kraus,[10] Graham,[20] Rienhoff [59] and others shown that this difference in response does not always hold true? Has it not been shown that every form of hyperplastic goiter, whether diffuse as in exophthalmic goiter or patchy and discrete as in toxic adenoma, will for a time respond to medication with iodine and be followed by marked improvement in clinical symptoms? Is it only the inability to produce exophthalmos experimentally by administration of thyroxin which finally distinguishes toxic adenoma from exophthalmic goiter? But has not even this final objection been overcome by numerous observations in the past and by the recent experimental results of Kunde,[66] who by means of thyroxin did succeed in producing the complete clinical picture of exophthalmic goiter, including exophthalmos?

If, as a whole, Plummer's hypothesis of toxic adenoma as fundamentally different from exophthalmic goiter is untenable, what clinical lessons of importance can be learned from a close study of the immense number of contributions on this most important problem? Briefly summarized, these lessons are:

1. Toxic adenoma and exophthalmic goiter are merely variations of a single disease. Eponymically, Parry's disease is the most appropriate designation, for Parry is the first observer who described all varieties of toxic goiter.

2. Clinically, a nodular goiter without exophthalmos may be as toxic or even more toxic than one with ocular manifestations. The prognosis in a severe case of toxic adenoma with myocardial insufficiency is much graver than in a moderately severe case of exophthalmic goiter with markedly bulging eyes, but with the myocardium fairly intact.

3. Although toxic adenoma may run as severe a course as exophthalmic goiter, its course is usually milder, and the surgical results are usually more satisfactory than in classic exophthalmic goiter.

4. The more favorable results in toxic adenoma are not due to any fundamental difference in nature from exophthalmic goiter but to a variation of a single disease. In exophthalmic goiter, the entire gland is diffusely involved in the pathologic process; hence, the symptoms are usually more marked and surgical resection is less satisfactory. In toxic adenoma, the thyroid gland shows one or several areas of involvement with intervening healthy tissue between the affected areas; hence, the symptoms are usually milder and surgical resection more satisfactory. However, it is only in about one third of the cases of toxic

66. Kunde, M. M.: Studies on Metabolism: Experimental Hyperthyroidism, Am. J. Physiol. **82:** 195, 1927.

adenoma at the Mayo Clinic that the lesion has been found single. In the majority of cases, the adenomas are scattered throughout the gland. Moreover, in a number of instances, the adenomas are in state of regression, while the intervening parenchyma may be the seat of the disease. Hence the practical deduction of almost all surgeons who perform operations on the thyroid glands has been that subtotal thyroidectomy as the method of choice is the treatment not only for exophthalmic goiter but also for toxic adenoma.

The Response of the Internists.—In contrast to the relatively large number of eminent surgeons whose vast personal experience with toxic adenoma had made them assail as untenable Plummer's theoretical and practical deductions about the dual nature of toxic goiter, is the small number of prominent internists who have joined the ranks of the dissenters. Plummer's dictum that toxic adenoma—adenoma with hyperthyroidism—is to be distinguished sharply from exophthalmic goiter both as a clinical and as a pathologic entity, and is to be considered essentially a surgical disease, found its staunchest adherents not only among the surgeons but also in the ranks of the internists. A review of medical publications, textbooks and systems of medicine shows almost a unanimous and unqualified acceptance of Plummer's teachings. Even internists who are in favor of submitting patients with severe cases of classic exophthalmic goiter to a course of medical treatment before referring them for operation are in favor of surgical intervention in toxic adenoma as soon as a positive diagnosis is made. Such an ardent advocate of the nonsurgical treatment for exophthalmic goiter as Bram,[67] who declared that he does not accept as rational any operative procedures on the thyroid in exophthalmic goiter except as an emergency measure when marked pressure phenomena threaten the life or comfort of the patient, is prompt to emphasize that toxic adenoma is from the start essentially a surgical disease.

What is the explanation for this apparently anomalous attitude of almost all internists toward toxic adenoma?

The explanations are many, but the chief reasons are threefold:

Clinical: The observation is that local attack on the thyroid by surgical measures does yield strikingly better results in toxic adenoma than by any medical measures undertaken either for this thyrotoxic condition or for typical exophthalmic goiter.

Pathologic: The prevailing view among the medical profession is that every tumor growth is essentially a surgical disease. Toxic adenoma having been recognized as a true tumor growth, except by a few dissen-

67. Bram, I.: Goiter, Nonsurgical Types and Treatment, New York, The Macmillan Company, 1924, pp. 218 and 269.

ters, logically must, as soon as the diagnosis is made, be referred by every conscientious internist to the surgeon for immediate removal of the tumor, which is the cause of the toxic symptoms.

Radiotherapeutic: There prevails an inadequate familiarity with the achievements of roentgen therapy and radium in the treatment of neoplastic conditions in general, and thyroid neoplastic conditions in particular.

The Response of the Roentgen Therapists.—In 1902, when the technic of roentgen therapy was in its earliest infancy, Williams [68] of Boston was the first to report: "I am using the x-rays for treating Parry's or Graves' disease, and thus far with encouraging results. The glands have diminished in size, and the general condition of the patients has improved."

Mary D., 26 years of age. Right lobe of thyroid gland 2x4 cm., left lobe 5x8 cm. After five exposures of twenty minutes each, given at intervals of about four days, the right lobe was 1½x2 cm., the left lobe 3¼x4 cm., and her general condition was much improved.

Two years later in 1904, Charles H. Mayo [69] reported a series of severe cases of exophthalmic goiter in patients who were poor surgical risks, but who had improved greatly after roentgen treatment. The patients were subsequently operated on succesfully, without the high mortality rate which obtained in the early years of such operations. The roentgen technic carried out by Mayo [70] was as follows: "The x-ray is applied over the gland for as many times as is sufficient to discolor or even burn the skin. This treatment is given until the general condition is improved and the operation is considered safe." Surely no experienced radiotherapist in recent years ever recommended such strenuous skin treatment in cases of exophthalmic goiter as Mayo did then. It is strange, therefore, that one fails to find any mention of those perithyroid adhesions which are often advanced by surgeons as one of the chief objections against resorting first to roentgen treatment in cases of exophthalmic goiter before subjecting the patient to the risks of an operation.

Several months later, in 1905, another noted American surgeon, Carl Beck [71] of New York, reported the value of roentgen therapy not

68. Williams, F. H.: The Roentgen Rays in Medicine and Surgery, New York, The Macmillan Company, 1902, p. 679.

69. Mayo, C. H.: Thyroidectomy for Exophthalmic Goiter, Based upon Forty Operative Cases, M. Rec. **66:** 734, 1904.

70. Mayo, C. H.: Goiter: Its Surgical Treatment Based on Four Hundred and Seventy-five Cases, Collected papers by the staff of St. Mary's Hospital, Mayo Clinic, 1905-1909, p. 446.

71. Beck, C.: Ueber die Kombination von Excisions- und Roentgen-Therapie bei Morbus basedowii, Berl. klin. Wchnschr. **42**:593, 1905.

only as a preoperative measure in cases of exophthalmic goiter in patients who were poor surgical risks, but also as a postoperative measure in patients on whom thyroidectomy had been performed and who failed to be benefited by the operation. So impressed was he with the favorable results of roentgen treatment in postoperative cases that he subjected a number of patients preoperatively to this treatment and kept delaying the use of the skilled surgeon's scalpel until it was found no longer necessary, the patients having recovered under the roentgen treatment. In subsequent studies,[72] in 1908 and 1909, he reported his results and then formulated his indications for roentgen therapy in treatment of patients with exophthalmic goiter.

1. In cases with moderate enlargement of the thyroid gland, irradiation only is advocated, without an operation. Thirty-six cases, or 72 per cent of his series of fifty patients, were thus successfully treated.

2. In cases in which marked enlargement of the thyroid gland occurs, partial excision followed by roentgen treatment is the method of choice.

3. In cases in which the patients have severe symptoms and are poor surgical risks, preoperative irridiation is to be used until the patient improves sufficiently to endure the risks of an operation.

The favorable results of these three American pioneers quickly paved the way for the adoption of roentgen treatment in cases of exophthalmic goiter throughout the entire world. And, in 1915, when Ludin[73] of Basel collected from the literature 208 publications dealing with roentgen treatment of exophthalmic goiter, every civilized country on the globe was well represented. The consensus of opinion of the majority of these investigators was that with properly applied technic and sufficient clinical experience as good results can be achieved by roentgen treatment as by surgical intervention.

With improvement in surgical technic the mortality was gradually lowered in some clinics, but even at the present day there is a surgical mortality. Moreover, not every patient who recovers from the immediate dangers of the operation is cured at once, as is believed in both lay and medical circles. On the other hand, with improvement in roentgen technic and greater clinical knowledge in the treatment of this disease, a number of roentgen therapists have reported from 75 to 100 per cent success in the treatment of their patients. Although every roentgen therapist has not been as fortunate in his results, yet a recent

72. Beck, C.: Partial Thyroidectomy Combined with Roentgen-Therapy in Basedow's Disease, Grad. M. J., 1908, vol. 25; Struma u. Morbus basedowii und die Behandlung dieser Krankheiten mittels Rontgenstrahlen, Fortschr. a. d. Geb. d. Röntgenstrahlen **15**:63, 1910.

73. Ludin, M.: Die Behandlung der Strumen und des Morbus basedowii mit Röntgenstrahlen Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **18**:205, 1914-1915.

review of the literature by Krause,[74] based on hundreds of carefully examined individual reports, places the average successful results at 82 per cent, practically the same figures as given by a careful analysis of the surgical results.

Having obtained such favorable results from roentgen therapy in the treatment of patients with exophthalmic goiter in whom the clinical course of the disease is usually more severe and the pathologic involvement of the gland more diffuse and extensive than in toxic adenoma, one should therefore have expected even better results in toxic adenoma than in exophthalmic goiter. Indeed, it has been the experience of roentgen therapists that in the milder or formes frustes of exophthalmic goiter, among which unwittingly many cases of toxic adenoma must have been included, the results are much more favorable than in the outspoken cases of the disease. Unfortunately, a careful review of the literature fails to reveal a single publication especially devoted to the results of roentgen treatment of toxic adenoma. Only an occasional casual remark is found stating either that toxic adenoma responds more favorably than straightforward exophthalmic goiter or that in a few cases of toxic adenoma the results were not favorable.

Why has roentgen therapy failed to come forward with an authoritative, informative answer in toxic adenoma as it has done in hundreds of publications on exophthalmic goiter? The answer is that the roentgen therapist is almost entirely conditioned in the type of cases he is called on to treat by the decision of his medical or surgical colleagues, and both of these have decided that as soon as a diagnosis of toxic adenoma of the thyroid is made the case becomes at once surgical.

But are the indications for surgical intervention always greater in cases of toxic adenoma than in cases of exophthalmic goiter? Are the phenomena of mechanical pressure in toxic adenomas so frequent and severe that from the outset of their characteristically slow growth and development these tumors are unsuitable and unamenable to roentgen therapy? If the toxicity, as has been granted by both surgeons and internists, is of slower development and less in degree than in exophthalmic goiter, are the pressure phenomena the chief contraindications to roentgen therapy? If so, one should frankly formulate contraindications along these more rational lines than merely make an arbitrary statement: Toxic adenoma is essentially a surgical disease. I shall then consider the efficiency of roentgen therapy to cope with the compression phenomena of toxic adenoma and decide by actual study of a series of such cases whether these contraindications are valid or not. I do know, however, from a study of the literature and my own obser-

74. Krause, P.: Die Röntgentherapie der Basedowschen Krankheit, Strahlentherapie **27**:393, 1927-1928.

vations that in toxic adenoma as in exophthalmic goiter it is most frequently, if not invariably, the toxic and not the compression phenomena that decide the issue of the case. Moreover, I do know that in cases of malignant tumors of the thyroid gland where invasive growth and compression phenomena are a much greater menace than in toxic adenoma of the thyroid, roentgen and radium therapy have yielded striking results. "Indeed," as stated in a recent publication,[75] "the results of radiotherapy in primary malignant tumors of the thyroid seemed so encouraging that a number of observers (Perthes,[76] Schadel,[77] Holfelder,[78] Holzknecht [79] and others stressed the superiority of radiotherapy over surgical intervention in treatment of fully developed thyroid cancer. Hence, I feel confident that with proper technic roentgen therapy should have yielded favorable results in toxic adenoma of the thyroid. I shall, however, not indulge in any further theoretical discussions what might have been accomplished by judicious roentgen therapy, but will proceed to present what has been accomplished by radium in the treatment of toxic adenoma of the thyroid.

The Response of the Radium Therapists.—In a recent study,[80] the literature was reviewed and a series of cases reported which "incontestably prove the value of radium in the treatment of Graves' disease. Clinical cure of a lasting kind has been obtained not only by implanting radium interstitially into the thyroid gland but equally as well by external applications of properly screened radium." Can similar results be achieved by radium therapy in toxic adenoma of the thyroid? The answer to this question forms the text of the subsequent part of this study.

RADIUM THERAPY

Encouraged by the brilliant therapeutic result achieved by the American surgeon, Abbe,[81] with the interstitial use of radium in a severe case of exophthalmic goiter in which a prominent surgeon had refused opera-

75. Ginsburg, S.: Bone Metastasis in Thyroid Tumors: Early Diagnosis and Radiotherapy, Am. J. Roentgenol. **18:** 203, 1927.

76. Perthes, J.: Zur Biologie und Klinik der Röntgentherapie der chirurgischen Krebse, Strahlentherapie **15:** 695, 1923.

77. Schadel, W.: Ueber Struma maligna, München. med. Wchnschr. **69:** 1282, 1922.

78. Holfelder, H.: Die Erfahrungen mit der Röntgentherapie der Malignen Tumoren an der Schmiedenschen Klinik, Strahlentherapie **15:** 715, 1923.

79. Holzknecht, G.: Schilddrusen Karzinom und Röntgenbestrahlung, Wien. klin. Wchnschr. **38:** 419, 1924.

80. Ginsburg, S.: Radium Treatment of Exophthalmic Goiter, to be published.

81. Abbe, R.: Exophthalmic Goiter Reduced by Radium, Arch. Roentg. Ray **9:** 214, 1904-1905.

tion, Wickham and Degrais,[82] in 1906, proceeded to use radium in the treatment of a patient with toxic adenoma of the thyroid. Instead of following Abbe's technic, they used a method which may be appropriate in the treatment of superficial skin lesions, but which was by no means calculated to affect a bulky toxic adenoma of the thyroid. Nevertheless, the result was much better than could have been anticipated. Not only did they obtain a reduction in the toxic manifestations of the disease but also a shrinkage of the adenoma.

With improvement in radium technic, it was readily demonstrated that highly favorable results can be achieved by the use of radium in cases of toxic adenoma just as well as in cases of classic exophthalmic goiter. What efficient radium therapy has achieved in the treatment of patients with exophthalmic goiter has been reviewed in a recent study. A careful perusal of the literature fails to show a single publication devoted especially to radium treatment of toxic adenoma. However, in the reports of Aikins,[83] Loucks,[84] Bower and Clarke [85] and Larkin,[86] many cases of toxic adenoma of the thyroid are mentioned in which treatment with radium was successful. Not only were the toxic symptoms relieved but the compression phenomena were also entirely removed.

Nevertheless, while radium treatment has been successful in many cases of toxic adenoma of the thyroid, the total number reported to date is still comparatively small. Hence, it will be of sufficient interest to submit a detailed report of the following eight cases from the radium clinic of the Beth Israel Hospital, during the years of from 1924 to 1927.

Case 1.—A woman, aged 44, married, was admitted to the radium clinic of Beth Israel Hospital on Feb. 3, 1925, complaining of weakness, irritability, progressive loss in weight, sleeplessness, enlargement in the right cervical region, hoarseness and cough of three years' duration. The previous history was unimportant. The present illness had its onset in 1921 with progressive weakness, anorexia and constipation. During the year previous to presentation at the clinic irritability, progressive loss in weight, sleeplessness and enlargement in the right cervical region had occurred; lately slight hoarseness and cough had developed.

82. Wickham, L., and Degrais, P.: Radiumtherapie, J. B. Baillière et fils, Paris, 1909.

83. Aikins, W. H. B.: Radium in Toxic Goiter, Am. J. Roentgenol. **7:** 404, 1920.

84. Loucks, R. E.: Radium Treatment of Toxic Goiter with Metabolic Deductions, Am. J. Roentgenol. **10:** 767, 1923; Radium Treatment of Thyrotoxicosis, Radiology **4:** 473, 1925; Clinical Evidence of Thyrotoxic Control after Radium Therapy, Am. J. Roentgenol. **18:** 509, 1927.

85. Bower, J. O., and Clarke, J. H.: Action of Radium on Diseased Thyroids in Man, Am. J. Roentgenol. **10:** 632, 1923.

86. Larkin, A. J.: Radium in Twenty Cases of Hyperthyroidism, Illinois M. J. **49:** 468, 1926.

Physical examination revealed in the right lobe of the thyroid gland just above the sternoclavicular junction an oval mass, 4 by 4 by 3 cm. in diameter, firm in consistency, moving with deglutition. The rest of the thyroid gland was apparently not enlarged. Bruit and thrill were absent. The heart and lungs were normal. The basal metabolic rate was plus 8.

The diagnosis was toxic adenoma of the thyroid.

Radium treatment was instituted. Between Sept. 14 and 27, 1925, the patient received 3,000 mg. hours of radium with the block (fig. 1) at 3 cm. distance over the tumor mass and another dosage of 3,000 mg. hours over the upper sternal region.

The result was the shrinkage of the adenoma to 3 by 3 by 2 cm. in size and subsidence of constitutional symptoms. At the last examination on May 5, 1927, the adenoma was shown to be stationary in size and the patient free from any toxic symptoms.

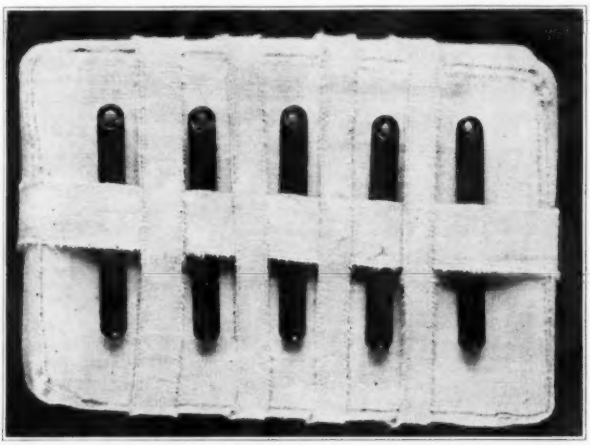

Fig. 1.—Radium block. The radium block is made of balsa wood. Its dimensions are 7 by 5 by 3 cm. It is covered by adhesive plaster. Several layers of gauze are interposed between it and the skin to serve as a cushion and to absorb perspiration. The distribution of the radium capsules is shown. Each brass capsule, 1 mm. thick, contains from 10 to 25 mg. of radium in the form of standard steel needles, according to indications. The block is strapped in place by means of adhesive plaster and reinforced with a bandage; 3,000 mg. hours constitute an erythema dose.

Comment.—Five important lessons taught by this comparatively simple case are:

1. Fairly marked, progressive, toxic constitutional symptoms may be present for a period of four years with a comparatively small toxic adenoma measuring 4 by 4 by 3 cm. This emphasizes again the important clinical observation that the degree of the enlargement of the thyroid in toxic goiter does not run parallel with the toxic manifesta-

tions. A bulky adenoma of ten, twenty or even forty years' standing may exist without constitutional symptoms. On the other hand, a small or even clinically impalpable toxic adenoma may give rise to fairly marked toxic constitutional symptoms.

2. Fairly marked toxic constitutional symptoms may be present for years with a comparatively low basal metabolic rate. Although the basal metabolic rate is one of the most reliable aids in gaging the degree of severity in cases of toxic goiter, every experienced worker in thyroid pathology knows that the severe cases may be at times accompanied by a low basal metabolism. In this machine-made age, when mechanical aids in diagnosis are frequently given the precedence over expert clinical observation and keen cerebration, the low basal metabolism associated with fairly marked toxic clinical symptoms in this case is a new reminder to correlate carefully all clinical and laboratory data and to be guided primarily by careful clinical diagnostic criteria.

3. The prompt response of toxic adenoma to a single erythema dose of radium treatment in this case may be noted. The prompt improvement which was striking in this case was not only exceedingly gratifying to the patient, but also taught the radium therapist the important lesson that in radium one has a bloodless, safe, efficient physical agent that can vie successfully with the surgeon's scalpel in its attack on toxic adenoma of the thyroid.

4. The persistence of the clinical cure nineteen months after a single radium treatment is another important consideration. A cure induced even by a single dose of radium may be lasting.

5. The shrinkage of the adenoma from 4 by 4 by 3 cm. to 3 by 3 by 2 cm. sufficed to cause the disappearance of all toxic constitutional symptoms. Evidently complete disappearance of a toxic adenoma is not necessary to induce clinical cure in toxic goiter. A small, moderate-sized, or even a bulky adenoma may be present without necessarily inducing toxic symptoms.

Case 2.—*History.*—Jacob B., aged 75, a porter, first came under observation at the radium clinic of Beth Israel Hospital on Feb. 5, 1925. His chief complaints were irregular enlargement of the neck, nervousness, weakness, loss in weight, dyspnea and palpitation on exertion, all of five years' duration.

In the summer of 1920 the patient noticed a painless lump, the size of a walnut, in the right lower cervical region. A few weeks later a similar lump was felt in the left lower cervical region. Slowly but progressively the lumps continued to increase in size and were followed by the development of dysphagia, choking sensation in the throat, nervousness, headache, weakness, palpitation, tachycardia and dyspnea on exertion, marked tremor of the hands and a loss of 30 pounds (13.6 Kg.) in weight. In July, 1924, a basal metabolic determination showed plus 25 per cent. During the latter part of the same year he was given several applications of small doses of radium to the thyroid, with apparent temporary improvement.

Physical Examination.—Examination presented a well developed old man, looking much younger than the stated age. In his entire bearing there was marked nervousness and tremulousness. His face was suffused with a dusky flush. He was undernourished but not cachetic. Ocular signs of exophthalmic goiter were absent. The thyroid gland showed a large tumor mass in each lateral lobe (fig. 2*A*). The left tumor mass was smooth, oval, elastic, nontender and movable. Its dimensions were 6 by 5 by 3 cm. The mass in the right lobe of the thyroid was much harder but was not nodular nor irregular. It was freely movable, not tender on palpation and measured 9 by 7 by 5 cm. The circumference of the neck through the seventh cervical vertebra and the center of the tumor masses was 41 cm. Bruit and thrill were absent. The heart was slightly enlarged. The sounds were distant but regular. The second aortic sound was accentuated, but murmurs and irregularities were not detected. The blood pressure was 170 systolic and 65 diastolic. The upper extremities showed a marked coarse tremor.

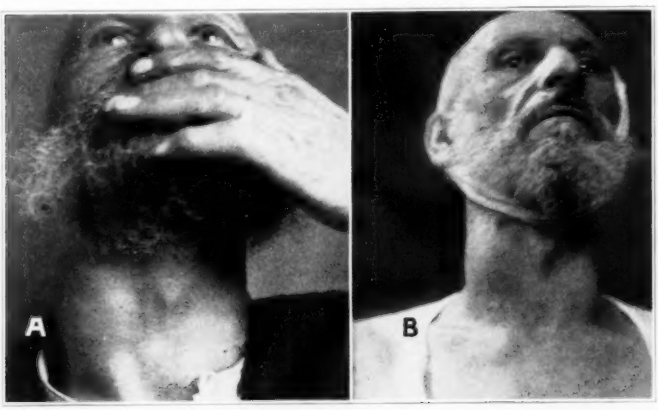

Fig. 2 (case 2).—*A*, toxic adenoma of the thyroid in a man, aged 75. Moderately severe toxic symptoms endured for five years. The basal metabolism was plus 25. The circumference of the neck was 40 cm. (July, 1924; before radium treatment). *B*, four months after radium treatment. There was relief of thyrotoxic symptoms, including disappearance of auricular fibrillation. Basal metabolism was normal. The circumference of the neck was reduced from 40 to 35 cm., with a simultaneous gain in weight (January, 1926).

Laboratory Data.—Roentgen examination of the chest showed slight enlargement of the cardiac shadow and a widening of the aortic arch. Electrocardiographic tracings were normal. The blood and urine were normal. The basal metabolism was plus 12 per cent. The diagnosis was toxic adenoma of the thyroid.

Course Under Observation Before Radium Treatment.—On Feb. 20, 1925, without any other discoverable cause except the condition of the thyroid, the patient developed auricular fibrillation. He was immediately ordered to rest in bed and was placed on moderate doses of digitalis. He improved gradually and about the middle of April, 1925, the heart action became regular. The improvement, however, was only temporary in duration, and the auricular fibrillation recurred with persistency of all the thyrotoxic symptoms.

Course Under Radium Treatment.—During the early part of May, 1925, he was given a dosage of 2,000 mg. hours of radium with the block at 3 cm. distance over each adenomatous mass. Within a few weeks there was moderate improvement in constitutional symptoms and a shrinkage of the adenomas. On June 18, 1925, auricular fibrillation was still present, but the patient felt stronger and the circumference of the neck showed a reduction from 41 to 36.5 cm. During the latter part of August, 1925, he was given 2,300 mg. of radium with the block at 3 cm. distance over the thymus region. This treatment was followed by further improvement in his general condition and a gain of 20 pounds (9 Kg.) in weight. Examination in January, 1926, found him in excellent condition. The auricular fibrillation had disappeared, and only an occasional extra systole was present. The circumference of the neck had shrunk from the original 41 to 35 cm. (fig. 2 *B*).

Further radium treatment was not given. The last examination in September, 1928, more than three years after the last radium treatment, showed the result unchanged.

Comment.—Whether this patient was too old for surgical intervention, I do not undertake to judge. I feel grateful, however, to his physician who forbade operation. This gave an opportunity to use radium therapy and to demonstrate the fact that in operations on patients who are poor surgical risks it is no longer necessary to "let nature take its course." The efficiency of radium put to the test in this case produced an excellent result practically amounting to a cure. The persistence of excellent results four years after treatment with radium was first started stresses the important lesson to the medical profession that the surgeon's scalpel is not the only means of attack against a toxic adenoma of the thyroid. Radium therapy efficiently used may give as good or even better result than surgical intervention without its attendant operative mortality, especially in the aged and feeble sufferers of toxic goiter.

Case 3.—*History.*—Rose W., aged 14, was referred to the radium clinic of Beth Israel Hospital in January, 1926, by Dr. B. Rosenbluth of New York, because of goiter, nervousness, irritability, loss in weight and insomnia, all of four months' duration. In October, 1925, four months before admission, the presence of a goiter was detected by the school nurse. The goiter kept fluctuating in size, but not until three months after its discovery were there any toxic symptoms noted.

Physical Examination.—Examination showed a well nourished and developed girl, aged 14, who weighed 96 pounds (43.5 Kg.). Her face was flushed. Her eyes were somewhat prominent, but exophthalmos was not definitely present. There were no other ocular signs of exophthalmic goiter. The thyroid gland showed a diffuse enlargement with predominant involvement of the isthmus and right lobe. The right lobe was firmer than the rest of the gland and felt distinctly nodular. A slight bruit was detected over the right lobe. Thrill was absent. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 33.5 cm. The heart showed moderate enlargement. The pulse rate was 140 per minute in the recumbent posture. Murmurs and irregularities were absent. The blood pressure was 120 systolic and 78 diastolic. The results of the rest of the examination were negative.

Laboratory Data.—Roentgen examination of the chest showed cardiac enlargement. Electrocardiographic tracings showed simple tachycardia, left ventricular predominance and the T wave inverted in lead 3. The blood and urine were normal. The basal metabolic rate was plus 14 per cent.

The diagnosis made was toxic adenoma of the thyroid.

Course Under Radium Treatment.—Radium treatment was started in February and was completed in April, 1926. The left lobe of the thyroid and the thymus received 2,300 mg. hours of radium each with the block at 3 cm. distance, while the right lobe of the thyroid was given 3,000 mg. hours. Improvement in subjective symptoms was noted at the end of April. Within five weeks after the first fractionated dose of radium was given her weight increased from 92 (41.7 Kg.) to 104.5 pounds (47.2 Kg.). The circumference of the neck was reduced to 33 cm. The heart showed only slight acceleration. Reexamination in February, 1927, found the patient completely free from any subjective complaints. She had gained 20 pounds (9 Kg.) in weight since her first admission to the radium clinic. Her neck had shrunk from the original 33.5 to 32.5 cm. There was still a slight bruit over the right lobe of the thyroid. Restudy with special reference to the need of any further radium treatment was suggested, but the patient considered herself well and saw no need to follow the recommendation. At the time of the last examination in August, 1928, the condition was practically unchanged.

Case 4.—*History.*—Rebecca S., aged 51, was admitted to the radium clinic of Beth Israel Hospital, March 9, 1926, complaining of a lump in the neck, nervousness, irritability, undue emotionalism, tremor, sleeplessness and loss in weight of five years' duration.

In 1921, five years before admission, her sister called her attention to the presence of a lump in the neck. Shortly thereafter she began to suffer from tremor, undue emotionalism, irritability, loss in weight and insomnia. During the past four years she consulted several physicians who diagnosed toxic goiter and prescribed internal medication, without any definite improvement in her symptoms.

Physical Examination.—Examination showed a well developed and nourished middle-aged woman weighing 128 pounds (57.1 Kg.). She appeared nervous and apprehensive. Her eyes were brilliant and presented a slight von Graefe's sign, but definite exophthalmos was absent. The tongue was slightly tremulous, the fingers markedly so. The thyroid gland showed an irregular enlargement of the isthmus and the left lobe. The right lobe was barely palpable. The mass was partly retrosternal and much firmer than normal. The skin was movable over it, but the growth seemed to be adherent to the deep cervical tissues. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 35.5 cm. The heart was slightly enlarged. The pulse rate was 120 per minute. Murmurs and irregularities were absent. Blood pressure was 130 systolic and 70 diastolic. The abdomen was moderately distended. The liver was enlarged and extended 5 cm. below the costal margin. The spleen and kidneys were not palpable. The lower extremities did not show edema.

Laboratory Data.—Roentgen examination of the chest showed a substernal thyroid with deviation of the trachea to the right. Electrocardiographic tracings revealed a simple tachycardia. The blood and urine were normal. The basal metabolic rate was plus 14 per cent.

The diagnosis was toxic adenoma of the thyroid, partly retrosternal, with deviation and compression of the trachea (fig. 3*A*).

Course Under Radium Treatment.—During the week of April 22 to 29, 1926, a dose of 3,000 mg. hours of radium with the block at 3 cm. distance was given

over the center of the mass. The result of this treatment was moderate improvement in constitutional symptoms and a shrinkage in the size of the neck from 35.5 to 33 cm. On June 9, 1926, without any increase in subjective complaints, a marked tachycardia was detected. Electrocardiographic examination revealed auricular flutter. The auricular rate was 300, the ventricular 150, giving thus a 2:1 heart block. How long this attack had lasted is unknown, for the case was

Fig. 3 (case 4).—*A*, toxic adenoma of the thyroid, partly retrosternal, in a woman, aged 51. Moderately severe toxic symptoms were endured for five years. The circumference of the neck was 35.5 (March, 1926; before radium treatment). *B*, thyrotoxic symptoms were relieved after radium therapy. The circumference of the neck was reduced from 35.5 to 31.75 cm. *C*, further reduction of the circumference of the neck from the original 35.5 to 30.75 cm., and a gain in weight of 11 pounds (5.4 Kg.) since admission to the radium clinic (February, 1928).

an ambulatory clinic case and the patient was not reexamined electrocardiographically until June 23, 1926. Auricular flutter was no longer present then; only a simple tachycardia persisted, and the P wave in leads 2 and 3 was high and notched.

In the meanwhile, commencing on June 19 and ending on July 20, another course of radium treatments was administered over the mass and over the upper retrosternal region. The result of this treatment was extremely gratifying. On July 27, 1926, only one week after the last fractionated dose of radium was given, the patient felt greatly improved in all her symptoms. She now felt strong enough to perform all her household duties without any undue fatigability. She felt fairly well until the fall of 1927, when a mild recrudescence occurred as the result of emotional stresses. A single course of radium treatments again controlled her symptoms. On the last examination in July, 1928, she was in fair health with marked shrinkage in size of the adenoma, and no intrathoracic compression symptoms were noted. The heart rate was only slightly above normal. Her basal metabolism rate was normal. The skin showed no atrophy or telangiectasis (fig. 3 *B*).

Comment.—The result achieved in this case by radium treatment reveals to every unbiased student of toxic adenoma of the thyroid that surgical intervention is no longer the only method of relief in dealing with this serious problem. This was a patient who had an outspoken condition of toxic retrosternal adenoma, of the thyroid with intrathoracic compression phenomena. At one time she developed an attack of auricular flutter with a rate of 300 and 2 : 1 heart block. Yet under radium treatment the thyrotoxic symptoms were controlled; the compression phenomena were relieved; the adenoma was shrunken to a fraction of its former size, and the patient was restored to a life of comparative usefulness and comfort without having been subjected to the dangers of an operation.

Case 5.—*History.*—Yetta K., aged 48, was referred to the radium clinic of Beth Israel Hospital, Dec. 7, 1926, by Dr. Max Weitzen of New York, complaining of symptoms of one year's duration consisting of progressive asthenia, palpitation, dyspnea, emotional instability, diarrhea, loss in weight, swelling of the neck, enlargement of the veins of the neck and of the upper part of the chest, cough, hoarseness and prolapsus ani.

In 1917, she developed weakness and palpitation on exertion. On examination, a "cystic" swelling about the size of a pigeon's egg was discovered in the right lobe—and a similar swelling about the size of an olive in the left lobe—of the thyroid gland. In July, 1917, the larger mass only was enucleated. The patient improved rapidly after the operation and felt apparently well until the end of 1925.

In December, 1925, following a period of emotional stress, she developed progressive asthenia, palpitation even at rest and marked dyspnea on exertion. She became irritable and unduly emotional, was annoyed by apparently causeless diarrheal stools and lost weight progressively. Six months later, in the summer of 1926, she noticed swelling of her neck and enlargement of the veins of the neck and the upper part of the chest. Her condition gradually grew worse, and she was finally referred to the radium clinic of Beth Israel on Dec. 7, 1926.

Physical Examination.—Physical examination showed a middle-aged woman, depressed, worn, slightly anemic and undernourished, weighing 118 pounds (53.5 Kg.). Exophthalmos and other ocular signs were absent. The tongue was tremulous. In the lower right cervical region there was a transverse, supple, nonadherent scar. The superficial veins over the lower anterior part of the neck and

the upper part of the chest were dilated (fig. 4 *A*), more markedly on the left than on the right. The thyroid gland showed a diffuse, irregular enlargement, more marked on the left than on the right. Consistency of the gland was firmer than normal. Bruit and thrill were absent. The circumference of the neck through the seventh cervical and the midthyroid region measured 34.5 cm. The heart was not enlarged. The pulse rate was 124 per minute. Murmurs and irregularities were absent. The blood pressure was 130 systolic and 80 diastolic. The results of the rest of the examination were essentially negative.

Laboratory Data.—Roentgen examination of the chest showed deviation and compression of the trachea to the right by a substernal thyroid. Electrocardiographic tracings showed simple tachycardia and the P wave notched in leads 2 and 3. Examination of the blood revealed: red blood cells, 3,300,000; hemoglobin content, 70 per cent; white blood cells, 5,500; polymorphonuclears, 50 per cent; large lymphocytes, 5 per cent; small lymphocytes, 45 per cent. The urine showed a trace of albumin and a few hyaline casts. The basal metabolic rate was plus 58 per cent.

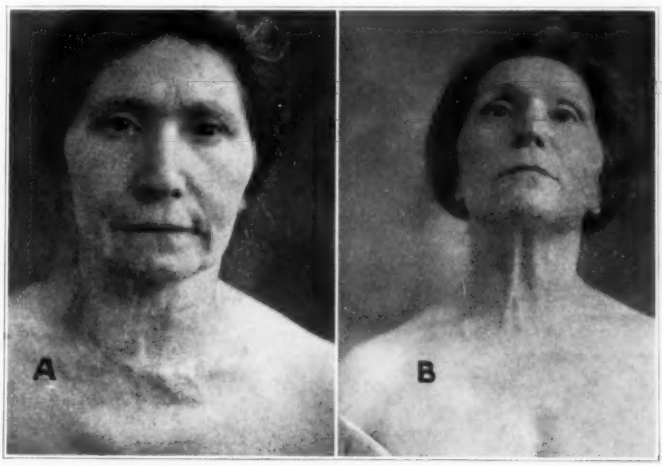

Fig. 4 (case 5).—*A*, postoperative recurrent toxic adenoma of the thyroid with mediastinal compression phenomena, as evidenced by enlarged veins over the neck and the upper anterior part of the chest. Moderately severe toxic symptoms endured for one year. The patient did not respond to medical treatment in addition to several roentgen treatments. The circumference of the neck was 34.5 cm. (December, 1926; before radium treatment). *B*, two weeks after the last application of radium. Marked improvement in constitutional symptoms resulted. There was a drop in basal metabolism of from plus 58 to plus 6, and a gain in weight of from 118 to 129 pounds (53.5 to 58.5 Kg.). With the shrinkage of the neck from 34.5 to 32.5 cm., dilatation of the veins over the neck and the anterior part of the neck was no longer present (July 28, 1927, after radium treatment).

Course Under Radium Treatment.—In January, 1927, 6,090 mg. hours of radium with the collar (fig. 8) at 3 cm. distance were given to the thyroid region and

3,700 mg. hours with the block at 3 cm. distance to the upper retrosternal region. The result was prompt improvement in subjective symptoms and a shrinkage of the neck from 34.5 to 33 cm. In the early part of March, 1927, two months after the first radium treatment had been given, her weight increased from 118 (53.5 Kg.) to 125 pounds (56.7 Kg.) but the tachycardia persisted. A restudy of the basal metabolism showed plus 58 per cent. Accordingly, at the beginning of June, 1927, radium treatment was repeated. The improvement this time was even more marked than after the first series of treatments. On July 20, only one week after the last fractionated dose of radium was given, her basal metabolism had dropped from plus 58 to plus 6 per cent. She felt much stronger. Her weight had increased to 129 pounds (58.5 Kg.). The pulse ranged between 84 and 90. The blood pressure was 125 systolic and 80 diastolic. The circumference of the neck showed a further reduction from the original 34.5 to 32.5 cm. The improvement was not confined, however, merely to the thyroid growth in the neck. The intra-

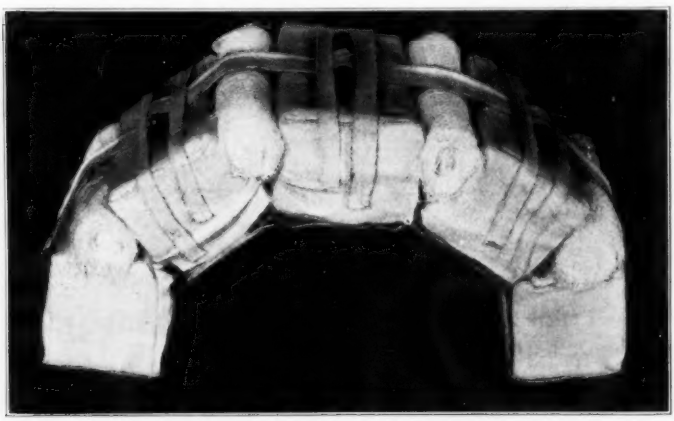

Fig. 5.—Radium collar. The radium collar is made of five blocks of balsa wood, each block measuring 5 by 3 by 3 cm. The blocks are held together by adhesive plaster. Their proper adjustment to the neck is obtained by pledgets of gauze. The distribution of the radium capsules is shown. Each brass capsule, 1 mm. thick, contains from 10 to 25 mg. of radium in the form of steel needles, according to indications. The collar is strapped in place by adhesive plaster and reinforced by a bandage; 6,000 mg. hours constitute an erythema dose.

thoracic retrosternal adenomatous mass must have been similarly affected, for the dilatation of the veins over the neck and the upper anterior part of the chest was no longer present (fig. 4 *B*).

Reexamination two months later showed that the patient was in good condition with a pulse rate of 72. She had been attending to her housework regularly. What is even more important, she had been subjected for almost two months to great emotional stress. One of her daughters had developed general sepsis and had been in a critical condition all this time. Moreover, during the same period her husband had succumbed to gastric cancer. Yet she stood well all these emotional stresses without any recrudescence of toxic symptoms. The last examination on

Aug. 2, 1928, found the improvement persisting in spite of active abdominal symptoms from a pathologically diseased gallbladder with a large, impassible stone demonstrated roentgenologically.

Comment.—The response to radium therapy in this case removes the chief objections to the treatment of toxic adenoma by radium. If such marked compression phenomena, as were present in this case can be removed by radium therapy, what contraindication then remains to its use in toxic adenoma of the thyroid?

CASE 6.—*History.*—Miss F. S. S., aged 40, a school teacher, was referred by Dr. D. A. Swick of New York on March 19, 1927, because of undue emotionalism, irritability, hoarseness, goiter, weakness, tachycardia, palpitation, diarrhea, loss in weight and sleeplessness of six years' duration. The present illness began six years prior to examination, in 1921, when she began to develop symptoms of thyrotoxicosis followed one year later by the appearance of a painless lump in the right side of the neck. Medical consultation led to a diagnosis of toxic goiter, and the patient was put through a regimen of rest, diet and internal medication. A brief period of improvement was followed by a prolonged relapse. And, although during the years from 1924 to 1927 she improved spontaneously, she was unable to resume her professional duties for more than a few hours a day and was frequently compelled to stay away from school for several days at a time.

When she was seen by me for the first time in March, 1927, she complained of all the symptoms enumerated.

Examination.—Physical examination presented a well nourished and developed young woman with flushed face and slightly prominent and brilliant eyes. There was only a suggestive von Graefe's sign, but no definite exophthalmos in spite of clinically perceived thyrotoxic symptoms of six years' duration. The scalp was normal, and there was an abundant growth of hair. Her skin was moist, and dermographia was easily elicited. The teeth were in good condition. The tongue was coated, fissured and tremulous. The pharynx was slightly congested.

Examination of the thyroid gland revealed in the right lobe and isthmus a large, oval, elastic mass measuring 10 by 6 by 4 cm. in size. The left lobe was slightly enlarged. The adenomatous mass was nontender, movable and not unduly vascular. Pulsation of the vessels in the neck was not increased. Bruit and thrill over the thyroid were absent. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 36 cm. The transverse diameter was from 14 to 15 cm.; the right vertical measured 6 cm.; the left, 4 cm.; the thickness of the right lobe was 4 cm., that of the left 2 cm.

The heart was not enlarged. There was a soft apical systolic murmur. The rate was 124 in the upright and 120 in the recumbent posture. The lungs did not show any abnormality. Results of the abdominal examination were negative except for a low median scar, the result of a gynecologic operation. There was moderate tremor of the fingers. The lower extremities were normal.

The basal metabolic rate was plus 29.

The diagnosis was toxic adenoma of the thyroid.

Course Under Radium Therapy.—Between April 2 and 16, 1927, the patient was given 6,000 mg. hours of radium to the thyroid with the radium collar at 3 cm. distance and 3,000 mg. hours to the thymus region with the block at 3 cm. distance. The results were extremely gratifying. On May 7, only five weeks after the first fractionated dose of radium was applied, and with a skin erythema

from the radium fully developed, she was subjectively free from symptoms. The pulse rate had dropped from 124 to 120 to 100 to 88. The circumference of the neck was reduced from 36 to 34.5 cm. and the adenoma measured 9 by 6 by 3. On June 28, she felt entirely well. For almost two months she had been able to attend to her professional duties without any fatigue. The school authorities had noticed the favorable change and complimented her "for not being absent a single day during this term." Her pulse rate was from 84 to 90. The adenoma had shrunk from 10 by 6 by 4 to 7 by 6 by 3 cm. She was seen again in September, 1927, and was found clinically well. In July, 1928, I was informed by Dr. Swick that the condition remained unchanged. During the entire year, she attended regularly to her professional duties and felt entirely well.

CASE 7.—*History.*—Rose B., aged 28, referred to the radium clinic of Beth Israel Hospital on Feb. 8, 1927, by Dr. Charles J. Brim of New York, had rapid enlargement of the thyroid gland, loss of 30 pounds (13.6 Kg.) in weight, nervousness, tremor, palpitation, dyspnea, hoarseness, dysphagia, marked asthenia, anorexia, diarrhea, cough, nausea and vomiting and night sweats of three months' duration. The present illness began in 1919, when, shortly after the birth of her first child, she noticed a slight prominence of the anterior region of the neck. This enlargement gave rise to no local discomfort and apparently remained stationary in size until the fall of 1926. Simultaneously with the growth in the neck she noticed a tendency to nervousness, accompanied during the last two years by slight progressive loss in weight. In November, 1926, she had an incomplete abortion followed by curettage. Eight days later, she developed signs of pneumonia and was ill for four weeks. When the pulmonary condition was improving, she noticed that the growth in her neck was enlarging rapidly. Presently she began to suffer from headaches, blurring of vision, dryness of mouth and lips, choking sensation in the throat, throbbing of the vessels in the neck, tachycardia and palpitation, dyspnea on exertion, anorexia and nausea, diarrhea, asthenia, disturbed sleep, night sweats, tremor, nervousness and irritability. Within three months after the onset of her symptoms, she lost 30 pounds (13.6 Kg.) in weight.

In spite of these complaints, she struggled along to take care of her four children and her household duties. At last her strength gave way, and she consulted Dr. Brim, who had her referred to the radium clinic on Feb. 8, 1927.

Examination.—Physical examination presented a young woman, nervous, restless, with a flushed face and prominent eyes, but without definite signs of exophthalmic goiter. There was a slight von Graefe's sign. Other ocular signs were absent. Her tongue was slightly tremulous, although the fingers showed marked tremor. The pharynx was slightly congested. The tonsils were moderately enlarged and congested and appeared diseased. There was slight visible pulsation of the carotid vessels.

Examination of the thyroid gland showed a diffuse enlargement with predominant involvement in the isthmus. A large area in the isthmus felt harder than the rest of the thyroid tissue and was suggestive of an adenoma surrounded by diffuse hyperplastic tissue. The gland was freely movable, both under the skin and over the underlying tissues. Thrill was absent although a bruit was present over the entire gland. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 36 cm. The transverse diameter was 14 cm.; the right vertical, 5 cm.; the left vertical, 4 cm.; the thickness of the right lobe was 3 cm., that of the left 2 cm. (fig. 6*A*).

Examination of the heart showed no enlargement, and the rate was 96 systolic and 100 diastolic. The apical sound was booming and the second aortic sound

was accentuated. Murmurs and irregularities were not detected. The blood pressure was 150 systolic and 60 diastolic. The lungs were normal.

Examination of the abdomen revealed the upper level at the fifth right interspace midclavicular line and the lower border 4 cm. below the costal margin. The surface was smooth, the edge sharp and nontender. The upper level of splenic dulness reached the seventh interspace left midaxillary line, the lower border was palpable from 2 to 3 cm. below the costal margin.

Results of rectal and vaginal examinations were negative.

Laboratory Data.—Roentgen examination of the chest showed the cardiac shadow enlarged to both sides. Electrocardiographic tracings showed left ventricular preponderance and tachycardia. The urine was normal. Examination of the blood revealed: red blood cells, 3,470,000; hemoglobins, 5 per cent; white blood cells, 7,100; polymorphonuclears, 44 per cent; large lymphocytes, 3 per cent; small lymphocytes, 51 per cent. The basal metabolism was plus 52 per cent.

The diagnosis was toxic adenoma of the thyroid with diffuse hyperplasia.

Fig. 6 (case 7).—*A*, toxic adenoma of the thyroid in a woman, aged 28. Mild toxic symptoms ensued for almost eight years; severe toxic symptoms for three months. Basal metabolism was plus 52. The circumference of the neck was 36 cm. (February, 1927; before radium treatment). *B*, four months after a single course of radium treatments to the thyroid region only. All toxic symptoms disappeared, and there was a great gain in weight. The pulse rate was 72. The basal metabolism was normal. The circumference of the neck was reduced from 36 to 33 cm. (Sept. 8, 1927; after radium treatment).

Course Under Radium Treatment.—Commencing on April 26 and ending May 1, 1927, the patient received one continuous radium treatment with the radium collar at 3 cm. distance over the adenoma as its center. The total dose delivered was 6,000 mg. hours. The result was one of the most favorable I have ever observed in the treatment of toxic goiter by radium. Within one month after the single radium treatment was given she felt sufficiently improved to perform her household duties without undue strain. She had lost almost all of her symptoms and had gained 3 pounds (1.4 Kg.) in weight while the circumference of her neck was reduced from 36 to 33 cm. Her pulse rate dropped to 84 per minute. A basal metabolic determination showed plus 4. Reexamination on July 5, 1927,

showed a pulse rate of 72 and blood pressure readings 110 systolic and 60 diastolic, a drop of forty points in the systolic pressure without any change in the diastolic. With the shrinkage in the diffuse hyperplasia of the thyroid gland a single, discrete, hard tumor mass could be distinctly outlined in the isthmus and right lobe of the thyroid (fig. 6 *B*).

The patient has been kept under observation since, and at no time has she shown any recurrence of toxic symptoms. The last examination in June, 1928, showed her weight to have returned to 155 pounds (70.3 Kg.), the best she ever weighed before the onset of her toxic symptoms.

Comment.—Striking results from a single radium treatment as shown in this case are seldom encountered in the clinically classic cases of diffuse hyperplastic toxic or exophthalmic goiter, while in cases of toxic adenoma more than once has a similar response been observed. Nor is the constitutional reaction from the application of radium as marked in the average case of toxic adenoma as it is in the diffuse involvement of exophthalmic goiter. Evidently the discrete involvement of the thyroid represented by a single toxic adenoma is a lesion favorable to attack not only by surgical intervention but by radium therapy as well.

Case 8.—*History.*—Beckie O., aged 32, was referred to the radium clinic of the Beth Israel Hospital on March 8, 1927, by Dr. Max Weitzen of New York. Her condition consisted of goiter, nervousness, tremor of the hands, recurring attacks of mental depression, flushes of heat, night sweats, paroxysmal attacks of cough, dyspnea and palpitation on exertion, headache, irritability, emotionalism and loss of 32 pounds (14.5 Kg.) in weight. The goiter had been present twenty-six years, while the toxic symptoms had endured seventeen years.

The mother and one sister had had enlargement of the thyroid gland for a number of years, apparently not accompanied by any constitutional symptoms.

At the age of 6 years the patient became aware of the presence of a lump in the lower part of the center of the neck, which ever since its first appearance had remained practically stationary in size. In 1910, when the patient was 15 years of age, she developed nervousness, tremor of the hands and recurring attacks of abdominal pain. After medical measures had been tried for a time with complete failure, she was advised to undergo appendectomy for a supposed chronic appendicitis. One year later, the appendix was removed, but the patient's symptoms remained unrelieved. In 1917, after the birth of her first child, she developed an attack of severe melancholia which lasted for a year and a half. Milder attacks had been recurring ever since. In 1925, two years before admission to the radium clinic, she suffered an acute grippal infection which left her with a burning sensation in the throat and noises in both ears. Her nervous symptoms gradually increased in severity. She had flushes of heat and night sweats. In January, 1926, a tonsillectomy was performed for the exceedingly annoying condition of the throat. Relief failed to follow. Instead, since the tonsillectomy she has had frequent paroxysmal attacks of cough and expectoration. Her appetite was poor. She has lost 32 pounds (14.5 Kg.) in weight during the past several years. She was extremely emotional and irritable and easily became depressed. During the past fourteen months, following the tonsillectomy, marked asthenia has been the predominant and most distressing symptom.

She was treated ineffectually by several physicians and was finally referred to the radium clinic of the Beth Israel Hospital on March 8, 1927.

Examination.—What struck one especially during the first glance at the patient was the exceedingly woebegone melancholic expression of the face (fig. 7*A*), which was not subdued by the marked flush in her cheeks. There was no exophthalmos in spite of a history of seventeen years of thyrotoxic symptoms and in spite of the unmistakable mental manifestations which have been stressed by some observers as an important diagnostic feature that distinguishes exophthalmic goiter from toxic adenoma of the thyroid.

Examination of the pharynx failed to reveal sufficient cause for the excessively distressing throat symptoms. Only a slight congestion was present. The tonsils were entirely absent, having been successfully enucleated without any apparent benefit to the patient. The tongue was not tremulous although the hands showed a fine tremor.

Examination of the thyroid gland showed an irregular nodular enlargement, especially of the isthmus. The gland was firmer than normal but was freely movable. Bruit and thrill were absent. The circumference of the neck through the seventh cervical vertebra and the midthyroid region measured 33 cm. The transverse diameter was 13 cm.; the right and left vertical vertebrae were 5 cm. each; the thickness, 2 cm.

The heart was not enlarged. There was simple tachycardia. The pulse rate was 104. The blood pressure was 120 systolic and 90 diastolic. The lungs were normal.

The abdomen showed an old appendectomy scar; otherwise it was normal.

Examination of the vagina showed a bilateral cervical laceration; the body of the uterus was normal. Results of the rectal examination were negative.

Laboratory Data.—Results of roentgen examination of the chest were negative. Electrocardiographic tracings showed simple tachycardia. Examination of the blood revealed: red blood cells, 3,750,000; hemoglobin, 75 per cent; white blood cells, 6,000; polymorphonuclears, 68 per cent; large lymphocytes, 2 per cent; small lymphocytes, 30 per cent. The urine was normal. The basal metabolic rate was plus 30 per cent.

The diagnosis was toxic adenoma of the thyroid of many years' duration, with marked mental manifestations recurring in attacks.

Course Under Radium Treatment.—On March 31 and April 6, 1927, 5,000 mg. hours of radium with the radium collar at 3 cm. distance were given to the thyroid region, and on April 19, 3,000 mg. hours with the block were applied to the thymus region. The result was extremely gratifying. Within one week after radium therapy was started, improvement in symptoms was noted. On May 3, 1927, only one month after the first application of radium was made, her only complaints were: cough, slight expectoration and oppression in the chest. She felt strong. Her depression was gone. Her mood became hopeful and more cheerful. She began to gain in weight. Her pulse rate dropped to 72 per minute. The circumference of the neck had shrunk from 33 to 30.5 cm. (fig. 7*B*).

Reexamination fifteen months later, in July, 1928, showed the improvement persisting. Her weight had increased to 132 pounds (59.9 Kg.). Her pulse and basal metabolism were normal. During this entire period of observation her attacks of melancholia failed to recur (fig. 7*C*).

Comment.—The most instructive features of this case were:

1. The discovery of the adenoma at the early age of 6 years.

2. The development of toxic constitutional and local abdominal symptoms nine years after the appearance of the adenoma. The thyro-

Fig. 7 (case 8).—*A*, toxic adenoma of the thyroid in a woman, aged 32. Toxic symptoms endured seventeen years, and were accompanied by marked mental manifestations recurring in attacks. The basal metabolism was plus 30. The circumference of the neck was 33 cm. (March, 1927; before radium treatment). *B*, three weeks after radium treatment to the thyroid and thymus regions. There was marked improvement in constitutional symptoms, and a decided change in facial expression. The pulse rate was 72. There was a gain in weight, and a shrinkage of the circumference of the neck from 33 to 30.5 cm. (May 10, 1927; after radium treatment). *C*, eleven months after a single course of radium treatments. The pulse and basal metabolism were normal. The patient gained 14 pounds (6.4 Kg.) in weight. Mental symptoms did not recur, and shrinkage of the neck persisted (March, 1928; after radium treatment).

toxic condition was apparently overlooked. A local diagnosis of chronic appendicitis lead to appendectomy which failed to produce any relief. A low-grade smouldering toxic process continued with little, if any, increase in the size of the adenoma.

3. The added stimulus of pregnancy and the difficult adjustment of an irritable thyrotoxic patient to the trials, tribulations and frictions of marital life fanned the smouldering thyrotoxic flame into increased activity. The brunt of the intoxication predominantly affected the sensitive cells of the affective centers. The result was an outbreak of acute melancholia which did not subside for a year and a half. She had a spontaneous remission, but did not fully recover from her thyrotoxic condition. She remained nervous and irritable. She lost weight, and suffered from dyspnea and palpitation and had mild recurrent attacks of depression.

4. An acute influenzal infection aggravated all her thyrotoxic symptoms and was followed by distressing throat symptoms. Focal tonsillar infection was diagnosed. Tonsillectomy was performed, but relief failed to follow.

5. Finally, after seventeen years of continuous thyrotoxic symptoms with attacks of melancholia and local phenomena of the throat, the patient received one application of radium to the thyroid and one to the thymus region, and relief from her thyrotoxic symptoms promptly ensued. A complete transformation occurred in her disposition. If one carefully examines figure 7, it will tell the accomplished result more eloquently than words can describe. It is clinical observations of this kind viewed by the light of radium therapy which force the unshakable conviction in one's mind that both in cases of classic exophthalmic goiter and in cases of toxic adenoma the brain and the rest of the nervous system and all the other systems in the body are only secondarily affected from a primarily diseased thyroid gland and not vice versa. Relief from thyrotoxic symptoms by local attack with radium on the thyroid speaks decidedly against the thyroid as a compensatory agent in either toxic adenoma or exophthalmic goiter. Boldly, in both conditions, it points unerringly to a diseased thyroid gland as the highly noxious destructive source from which toxic products emanate and flood the system and exert their most baneful and pernicious effects on all loci minoris resistentiae.

SUMMARY AND CONCLUSIONS

In his illuminating study of thyroid adenoma, one of the foremost American students [87] in health and disease of the thyroid gland

87. Marine, D.: Benign Epithelial Tumors of the Thyroid Gland, J. M. Research **22**: 229, 1912-1913.

stated: "The term . . . thyroid adenoma . . . was formerly used by Rokitansky,[88] Virchow,[89] and Wolfler[90] to include symmetrical hyperplasias of the whole gland. . . . While at present there is a tendency to sharply distinguish morphologically between adenoma and diffuse overgrowth of the thyroid (goiter) and to criticize the earlier observers' use of the term 'adenoma;' nevertheless, the more extensive one's acquaintance with these growths becomes the more one is convinced that the point of the earlier writers was well taken; that there is no sharp division between benign epithelial tumors and diffuse overgrowths that some have been led to expect either anatomically or functionally."

In common with Marine[87] I fully endorse the views of the old masters in thyroid pathology and, therefore readily accept Aschoff's teachings that nodular goiter is synonymous with adenomatous goiter or adenoma of the thyroid, and that toxic nodular goiter is equally synonymous with toxic adenomatous goiter or toxic adenoma of the thyroid. Hence, clinically, a tentative diagnosis of toxic adenoma of the thyroid is warranted whenever a nodular goiter is associated with the constitutional symptoms of exophthalmic goiter with or without the ocular manifestations of the disease.

In recognizing toxic adenoma as a clinical-pathologic concept, I wish to stress strongly that neither clinically nor pathologically do I perceive any fundamental distinction between toxic adenoma and exophthalmic goiter except as the variation of a single disease. Nevertheless, for practical diagnostic and therapeutic reasons, the recognition of this variation is important, for in toxic adenoma the ocular signs are rarely present, the adenoma or adenomas may be small and readily disregarded if stress on this variation of thyrotoxicosis is omitted from the medical literature.

Eponymically, Parry's disease—and not Basedow's or Graves' disease—is the most appropriate designation for both toxic adenoma and exophthalmic goiter, for Parry was the first observer who described all varieties of toxic goiter.

Clinically, a nodular goiter without exophthalmos may be as toxic or even more toxic than a smooth, diffusely enlarged, or exophthalmic goiter with pronounced ocular signs. The prognosis in a severe case of toxic adenoma with myocardial insufficiency is much graver than that in a moderately severe case of classic exophthalmic goiter in which the patient has markedly bulging eyes and a fairly intact myocardium.

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88. Rokitansky, C.: Zur Anatomie des Kropfes, Wien, 1849, cited by Marine.

89. Virchow, R.: Die krankhaften Geschwulste, 1863, vol. 3, p. 15.

90. Wolfler, A.: Ueber die Entwickelung und den Bau des Kropfes, Arch. f. klin. Chir. **29**: 1, 1883.

Although toxic adenoma may run as severe a course as exophthalmic goiter, its clinical manifestations are usually milder, and the surgical results are more satisfactory than in classic exophthalmic goiter.

The more favorable surgical results in toxic adenoma are due not to any fundamental difference in nature from exophthalmic goiter but to a variation of a single disease: In exophthalmic goiter, generally the entire gland is diffusely involved in the pathologic process, while in toxic adenoma of the thyroid the gland shows one or several pathologic foci with intervening healthy tissue between the affected areas. Hence, generally, the symptoms are milder, and surgical resection is more satisfactory than in exophthalmic goiter.

Surgical intervention, however, is no longer the only efficient means in the successful treatment of toxic adenoma of the thyroid. The same factors which are operative to make surgical intervention more successful in toxic adenoma than in exophthalmic goiter are equally operative in roentgen and radium therapy.

Of these two methods surgical intervention has been recognized until the present day by the majority of the medical profession as the method of choice, while roentgen and radium therapy have been slighted or rejected.

A review of the literature and my own observations fully justify the following conclusions:

Surgical intervention is no longer the only means of relief in dealing with toxic adenoma of the thyroid.

Radium therapy efficiently applied not only removes the thyrotoxic symptoms but also shrinks the tumor growth and thereby removes the compression phenomena of toxic adenoma of the thyroid.

Radium therapy, safe, efficient, free from surgical mortality, deserves first choice not only in dealing with exophthalmic goiter but also in the treatment of toxic adenoma of the thyroid.

Finally, it must not be forgotten, to obtain the best results in toxic adenoma as well as in exophthalmic goiter a combination of radium therapy plus rest in bed, proper diet and medication, is highly desirable.

THE EFFECT OF THE PURINE BASE DIURETICS ON THE CORONARY FLOW *

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Reports based on experimental work concerning the effect of the salts of theobromine and caffeine, and later of theophylline, on the volume flow in the coronary arteries, began to appear shortly after the clinical report of Askanazy [1] in 1895. Taken as a whole, the collective evidence points definitely to a vasodilator action of these drugs on the coronary vessels. The work has been done almost entirely on preparations of the isolated heart, and with suspension preparations of arterial strips. While, for the most part, the results of such experiments can safely be taken as evidence of the actual pharmacologic effect of the drug clinically, there are certain objections. Especially is this true when there is a possibility that the action is a direct one on the vessel wall. In perfusion experiments a constant supply of the drug is reaching the tissues in a fixed dilution, permitting any amount to be taken up by the tissues in time. When a dose of the drug calculated to make the same dilution in the blood is injected into the circulation, one does not know how much is taken up by the tissues elsewhere, how quickly, or what the dilution is when it reaches the tissues to be tested; nor does one know what biochemical reaction in the blood may alter its action. In the isolated heart also, the vessel is free from the constant vasomotor changes present in the intact animal which might alter the response.

The only work on the intact animal available to us has been that of Sakai and Saneyoshi.[2] Their conclusion was that the vasodilator effects which they found may be ascribed to doses larger than those used clinically, and are referable to a rise in blood pressure.

For the past several years these drugs, and especially the salts of the obromine have been used in the Sunday morning clinic for patients with diseases of the heart at St. Luke's Hospital. The results are reported elsewhere by Gilbert and Kerr.[3] Some degree of relief from the anginal

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* From the Medical Department of Northwestern University.

1. Askanazy: Deutsches Arch. f. klin. Med. **56**:209, 1895.

2. Sakai and Saneyoshi: Arch. f. d. ges. Physiol. **78**:331, 1915.

3. Gilbert, N. C., and Kerr, John Austin: Clinical Results in Treatment of Angina Pectoris with the Purine-Base Diuretics, J. A. M. A. **92**:201 (Jan. 19) 1929.

pain was obtained in more than half of the cases, and in a few cases the relief was almost complete. The unpleasant symptoms which sometimes accompany the use of these drugs was somewhat deterrent; this, however, could be obviated in most of the cases by a change in the preparations used and in the method of administration. The good results were obtained just when they would be expected: when there was the largest element of probable vasomotor spasm, and the least element of anatomic change in the vessels.

Because of what we considered good clinical results with the drugs, and because the previous experimental work could not be considered altogether conclusive, it was determined to attempt further experimental work. The results are given briefly.

EXPERIMENTAL WORK

Direct measurement of the return flow in the coronary arteries in the intact animal must necessarily present many variables which are unknown. The operative procedures, the shock, and especially the traumatized thorax and open chest, are doubtless productive of changes in the basic condtions. Biochemical conditions in the blood may vary during the experiment with variations in the pulmonary ventilation, with the amount of saline introduced into the circulation and with other factors. But there is no variable which could be assumed to facilitate the action of vasodilator drugs.

Since the coronary flow is a direct function of blood pressure, and especially diastolic pressure, it would be demanded that this factor be controlled. The experiments recorded in this paper, with a few minor exceptions, resulted in a fall of both systolic and diastolic pressure, and rendered the control of this variable unnecessary. Variations of rate, as well as of other factors, such as venous inflow and tonus, have been shown by others to have no effect on the coronary flow when within ordinary limits (Anrep[4]).

In the experiments reported, dogs weighing about 6 Kg. were used. For the most part the Grehant anesthetic was used, a 5 per cent solution of chloroform in equal parts of alcohol and water. About 8 cc. per kilogram of body weight was administered through a stomach tube, preceded one-half hour by 0.01 cc. of morphine per kilogram of body weight. The dosage was varied slightly in proportion to the condition of the animal. On six dogs, chloretone in dosages of from 0.25 to 0.30 cc. per kilogram was used. On two dogs, ether was used, and in one case paraldehyde.

4. Anrep, G. V.: Physiol. Rev. **6**:596, 1926.

Blood pressure was recorded by means of a mercury manometer connected with the carotid. In a few cases a Huerthle apparatus was used, but this was discarded in favor of the mercury instrument.

The chest was opened to the right of the midline through the costal cartilages, and artificial ventilation was instituted. The cannula described by Morovitz [5] was slightly modified by introducing in the distal third enough of a curve so that when it was fixed in position in the coronary

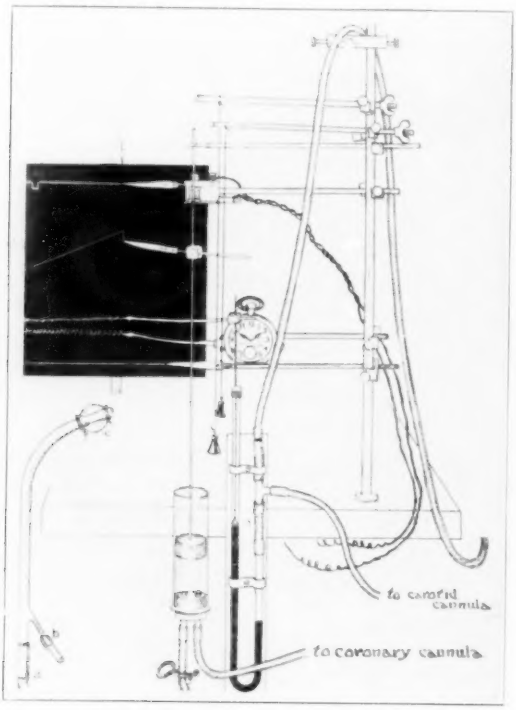

Fig. 1.—Apparatus for recording coronary flow and modified Morovitz cannula.

sinus, the cannula would project out through the midline without exerting pressure on the heart or lungs; otherwise, it was used as described by Morovitz. The cannula was connected with the cylinder of a piston recorder, placed lower than the heart, and the rise of the fluid level in the cylinder was traced on a revolving drum. Slight changes in the rate of flow were shown by deviations from the straight gradient of ascent.

5. Morovitz and Zahn: Deutsches Arch. f. klin. Med. **116**:366, 1914.

The cylinder was emptied manually at intervals, and the blood returned through a warmed cylinder connected with the femoral vein. The height of the cylinder was adjusted so as to permit of a constant return flow. Small variations in return flow are shown at once by changes in blood pressure and consequent changes in the rate of coronary flow. No experiments are recorded in which the cannula was not firmly seated in the coronary sinus at autopsy. While the return flow from the coronary sinus measures approximately only about three fifths of the total coronary flow, and there are variations from this ratio, the ratio remains

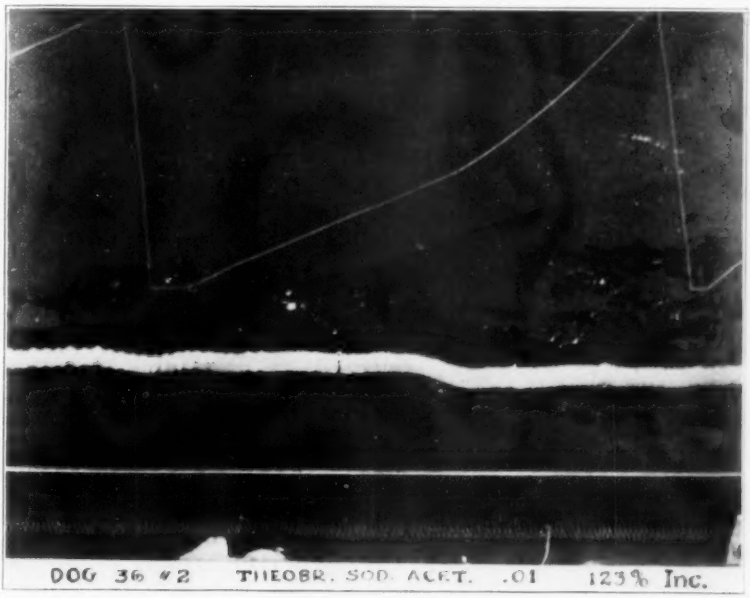

Fig. 2.—Section of tracing, showing effect of the injection of 0.01 cc. per kilogram of body weight of theobromine sodium acetate.

constant for the individual animal in the experiment (Lovatt-Evans and Starling [6]).

The drug was introduced through the cannula in the femoral vein. When dilutions of the drug in the blood are given in the tables, the rate of injection was such as to permit of one or more circulatory cycles during injection; otherwise, the drug was injected rapidly. Control experiments with distilled water and tap water showed no effect on the coronary flow.

6. Lovatt-Evans and Starling: J. Physiol. **46**:413, 1913.

The doses used were average human doses corresponding to those suitable for a man weighing 75 Kg. In the case of administration of theophylline ethylenediamine, the 0.1 Gm. (1½ grains) tablets were used clinically with good results, and part of the experiments were based on this dosage. The ampules furnished contain 0.48 cc., and in part of the experiments the larger dosage was used.

In considering the results of the administration of any of the drugs here used, it is to be borne in mind that we do not know the state of dilatation when the drug is injected, as we do not know what factors are opposing further dilatation. Also, a vasodilator drug previously injected may influence the results obtained from the injection of other vasodilator drugs for an unknown period afterward. The effect of the second injection may be slight or absent because of an extreme dilatation

TABLE 1.—*Effects of Injections of Caffeine Sodium Benzoate*

Dog	Experiment	Anesthetic	Dose per Kg.*	Dilution	Time of Injection	Effect: Blood Pressure: Systolic	Effect: Blood Pressure: Diastolic	Effect: Pulse	Per Cent Increase in Flow
52	2	Grehant	0.01	1:7700	35′	0	0	0	9.2
52	3	Grehant	0.01	1:7700	23′	— 5.5	— 4.5	+ 3	0
52	10	Grehant	0.01	1:7700	5′	0	0	—12	12.5
33	4	Grehant	0.0086	.....	...	—15	—16	— 9	0
53	2	Grehant	0.0083	1:9240	35′	+ 8	+ 6	— 3	16.7
43	2	Grehant	0.0082	.....	...	—18	—18	+ 9	15.4
42	1	Grehant	0.0071	.....	...	— 9	— 9	+ 7	0
33	2	Grehant	0.0066	.....	...	— 4	— 3	+12	0
41	1	Grehant	0.0066	.....	...	—25	—24	+18	20
29	10	Grehant	0.0066	.....	...	....	....	....	0
43	1	Grehant	0.0041	.....	...	—16	—14	+18	8.3
49	1	Grehant	0.0032	.....	...	—10.5	—11.5	+ 9	8.3

* Dose, 0.0067 cc. per kilogram; for a man weighing 75 Kg., 7½ grains (0.5 Gm.).

secured by the first injection. Or, when small doses are used, an increased response may be elicited by subsequent doses when the concentration of the drug in the blood is increased. Because of this, only in the first experiment in each dog is there no possibility of influence by the previous injection of drugs.

The results obtained with injections of caffeine sodium benzoate are shown in table 1. The effect of this drug on the coronary flow was less than with any of the other preparations. In dog 42, there was no response in the first experiment with what would correspond to a full human dose. There was not, however, the fall in flow which might be anticipated from the fall in blood pressure. That there was not already a vasodilatation at the time of injection is shown by the fact that a rather large dose of euphyllin (0.007 cc. per kilogram of body weight) gave an increase in flow of 100 per cent ten minutes later. In two cases there was an increase in flow with fractional doses in the first experiment. With the exception of one case (dog 53), the blood pressure fell. The pulse rate was accelerated in seven of the eleven cases.

Injections of theocine sodium acetate (table 2) showed a more marked effect on the flow than was experienced when caffeine sodium benzoate was used. In dog 44, there was an increase of 30 per cent in the flow with one half of the estimated human equivalent. In two cases there was no response. In dog 29, approximately a full dose was given five minutes after a 58 per cent response had been obtained with theobromine sodium acetate. There was a decrease in coronary flow, as might be expected in the presence of a preexisting vasodilatation and a fall in pressure. In dog 45, there was also no increase in coronary flow. The experiment was made eighteen minutes after a 120 per cent increase in flow had been caused by another drug.

A fall in pressure and an increase in pulse rate was again observed in most of the experiments. The smaller doses in the last two experiments did not cause a fall in pressure, but caused a rise, as did the almost full dose in dog 30.

TABLE 2.—*Effects of Injections of Theocine Sodium Acetate*

Dog	Experiment	Anesthetic	Dose per Kg.*	Effect			
				Blood Pressure			Per Cent Increase in Flow
				Systolic	Diastolic	Pulse	
45	6	Grehant	0.0038	— 4	0	+15	28.5
34	7	Grehant	0.0036	— 6	— 7	+ 6	34.5
39	2	Grehant	0.0035	— 8	—10	+20	28.5
44	2	Grehant	0.00336	— 7	— 5	+ 9	27.3
29	2	Grehant	0.0033†	— 6	— 8	— 3	—4.5
28	5	Grehant	0.0033	— 8	—10	+36	9.5
30	1	Grehant	0.0033	+10	+ 5	+ 3	21.4
26	5	Grehant	0.0033	0	0	0	3.3
45	4	Grehant	0.0019‡	—10	—10	+13	0
44	1	Grehant	0.0017	+ 2	+ 2	+ 6	30.7
39	1	Grehant	0.0016	+ 3	+ 5	+ 3	0

* Dose, 0.0035 cc. per kilogram; for a man weighing 75 Kg., 4 grains (0.26 Gm.).
† After large response with theobromine sodium acetate.
‡ After extreme previous dilatation.

The advantage of the vasodilator effect of the ethylenediamine in addition to that of the theophylline (theocine) is claimed for euphyllin (theophylline ethylenediamine). While we did not obtain as uniformly good results as those obtained by Guggenheimer and Sassa,[7] or Iwai and Sassa [8] in perfusion experiments on the empty beating heart, the effect was distinctly superior to that produced by theocine sodium acetate (table 3).

When there is as great a variability in results as must always obtain in work on the intact animal, it is possible that in a larger series of animals comparable results would have been obtained with the smaller

7. Guggenheimer and Sassa: Verhandlungen der deutschen Gesellschaft für innere Medizin, 35 Kongress, Wien., 1923, p. 101.

8. Iwai and Sassa: Arch. f. exper. Path. u. Pharmakol. **99**:215, 1923.

doses and greater dilution. As it was, experiment 1 in dog 63 showed a 25 per cent increase in flow with one half of the smallest human dose, and an estimated dilution in the blood of from 1 to 110,000.

The results obtained with theobromine and with its sodium acetate and sodium salicylate salts are shown in tables 4, 5 and 6. A greater

TABLE 3.—*Effects of Injection of Euphyllin*

Dog	Experiment	Anesthetic	Dose per Kg.*	Dilution	Time of Injection	Effect: Blood Pressure: Systolic	Effect: Blood Pressure: Diastolic	Effect: Pulse	Per Cent Increase in Flow
56	2	Ether	0.008	.....	...	−34	−30	+28	29.5
56	3	Ether	0.008	.....	...	−13	−13	+36	40
43	4	Grehant	0.0077	.....	...	−10	−10	0	18.75
42	2	Grehant	0.007	.....	...	−14	−11	+ 2	100
48	6	Grehant	0.0058	.....	...	− 7	− 7	−12	7.15
48	4	Grehant	0.0029	.....	...	− 6	− 5	+18	37.5
58	3	Ether	0.0028	.....	...	−18	−18	0	−12.5
59	5	Grehant	0.0028	1:26,813	10′	−12	− 9	+24	50
57	3	Grehant	0.002	.....	...	− 6	− 6	+12	50
57	4	Grehant	0.002	.....	...	− 6	− 6	+51	40
48	5	Grehant	0.0015	.....	...	− 8	− 8	0	7.7
59	6	Grehant	0.0014	1:53,626	12′	− 8	− 7	+ 6	9.2
60	4	Grehant	0.00095	1:82,134	15′	+ 1	+ 1	0	9.5
60	3	Grehant	0.00076	1:102,067	8′	0	0	+ 9	0
60	2	Grehant	0.00038	1:205,334	15′	0	0	0	0
60	1	Grehant	0.00019	.....	...	0	0	0	0
61	1	Grehant	0.0003	.....	...	+ 4	+ 4	0	0
61	2	Grehant	0.0006	.....	...	− 4	− 4	+18	0
61	3	Grehant	0.0006	.....	...	− 2	− 2	0	0
61	6	Grehant	0.0012	1:64,167	0′	+ 2	+ 2	+ 3	20
61	7	Grehant	0.0012	1:64,167	13′	+ 2	+ 2	+ 3	25
63	1	Grehant	0.0007	1:110,367	8′	+ 6	+ 6	−15	25
63	2	Grehant	0.0014	1:55,188	17′	0	0	0	50

* (Ampules) 0.0004 cc. per kilogram; for a man weighing 75 Kg., 7½ grains (0.48 Gm.).
(Tablets) 0.0013 cc. per kilogram; for a man weighing 75 Kg., 1½ grains (0.1 Gm.).

TABLE 4.—*Effects of Injection of Theobromine*

Dog	Experiment	Anesthetic	Dose per Kg.*	Dilution	Time of Injection	Effect: Blood Pressure: Systolic	Effect: Blood Pressure: Diastolic	Effect: Pulse	Per Cent Increase in Flow
57	2	Grehant	0.005	1:15,400	34′	+ 2	0	−12	33.5
58	1	Ether	0.0037	1:84,000	58′	−16	−16	− 3	78
58	6	Ether	0.0037	1:84,000	40′	+ 2	+ 2	0	5.25
63	3	Grehant	0.0012	1:66,220	32′	+ 2	+ 2	0	33
63	4	Grehant	0.00248	1:33,110	35′	− 4	− 4	+18	33
63	5	Grehant	0.005	1:16,555	47′	−10	0	+ 9	72.72

* Dose, 0.005 cc. per kilogram; for a man weighing 75 Kg., 6 grains (0.38 Gm.).

and more constant increase in the return flow through the coronary sinus resulted with the use of these drugs. This increase in flow was observed not only with the estimated dosage in every instance except when there was a previous extreme vasodilatation, but also with proportionate doses down to one eighth. Here again there was observed a decrease in systolic and diastolic blood pressure, with an increase in the pulse rate in most of the experiments. The exceptions were more frequent with the smaller doses.

TABLE 5.—*Effects of Injection of Theobromine Sodium Salicylate*

Dog	Experiment	Anesthetic	Dose per Kg.*	Dilution	Time of Injection	Effect: Blood Pressure: Systolic	Effect: Blood Pressure: Diastolic	Effect: Pulse	Per Cent Increase in Flow
17	7	Paraldehyde	0.035	.....	...	0	0	....	16.7
14	4	Chloretone	0.03	.....	...	0	0	+ 9	0
9	5	Chloretone	0.026	.....	...	− 4	− 2	+ 6	15.4
12	3	Chloretone	0.024	.....	...	− 8	− 4	+21	66.6
12	5	Chloretone	0.024	.....	...	+ 4	+ 2	−12	37.75
12	11	Chloretone	0.024	.....	...	− 6	− 2	− 6	25
12	12	Chloretone	0.024	.....	...	+ 4	....	− 3	54.5
23	1	Grehant	0.0177	.....	...	−23	− 8	− 6	50
23	5	Grehant	0.0177	.....	...	− 8	− 2	− 9	83.7
17	1	Paraldehyde	0.0175	.....	...	− 1	0	− 7	25
18	3	Grehant	0.0167	.....	...	−14	....	....	33
20	6	Grehant	0.0166	.....	...	− 4	− 2	+18	47
20	1	Grehant	0.0166	.....	...	− 8	− 6	+27	32.2
15	1	Chloretone	0.0145	.....	...	+ 2	− 2	+ 3	25
14	1	Chloretone	0.0135	.....	...	0	0	0	0
14	2	Chloretone	0.0135	.....	...	0	0	0	0
14	7	Chloretone	0.0135	.....	...	0	0	+ 6	0
14	8	Chloretone	0.0135	.....	...	0	0	0	0
9	2	Chloretone	0.013	.....	...	− 1	− 1	+24	22
44	6	Grehant	0.01	.....	...	− 4	− 4	+24	51.5
34	3	Grehant	0.011	.....	...	−14	−10	− 3	13
37	1	Grehant	0.011	.....	...	− 4	− 3	+ 3	40
35	3	Grehant	0.01	.....	...	+ 4	− 7	− 3	37.5
35	4	Grehant	0.01	.....	...	− 6	−14	+ 6	25
39	4	Grehant	0.01	.....	...	− 6	0	+30	18.75
41	2	Grehant	0.01	.....	...	−11	−12	+18	36.4
33	5	Grehant	0.01	.....	...	− 7	−11	0	4.5
28	1	Grehant	0.01	.....	...	−28	−23	+36	154.3
30	2	Grehant	0.01	.....	...	−24	−24	+18	0
30	5	Grehant	0.01	.....	...	−10	−10	+ 9	38.5
26	1	Grehant	0.01	.....	...	− 4	− 3	+30	28.6
52	11	Grehant	0.01	1:7700	15′	0	0	+ 9	21.5
54	7	Grehant	0.01	.....	...	0	+ 2	−12	15.4
55	2	Grehant	0.008	.....	...	+20	+20	+ 3	60
56	1	Ether	0.005	.....	...	+ 2	+ 4	0	29.5
54	2	Grehant	0.004	1:18,360	15′	0	0	0	50
58	2	Ether	0.0035	.....	...	−12	−12	+ 9	27
53	1	Grehant	0.00125	.....	...	+10	+10	+ 3	16.7
54	1	Grehant	0.00125	.....	...	0	0	0	0

* Dose, 0.01 cc. per kilogram; for a man weighing 75 Kg., 11¼ grains (0.75 Gm.).

TABLE 6.—*Effects of Injections of Theobromine Sodium Acetate*

Dog	Experiment	Anesthetic	Dose per Kg.*	Dilution	Time of Injection	Effect: Blood Pressure: Systolic	Effect: Blood Pressure: Diastolic	Effect: Pulse	Per Cent Increase in Flow
9	10	Chloretone	0.0214	.....	...	0	0	0	0
9	13	Chloretone	0.0214	.....	...	0	0	0	Slight fall
29	1	Grehant	0.0103	.....	...	− 8	− 4	0	58.4
38	1	Grehant	0.01	.....	...	....	....	−18	52.9
35	2	Grehant	0.01	.....	...	− 9	− 7	+12	123
40	5	Grehant	0.01	.....	...	+12	+11	− 6	122.3
28	8	Grehant	0.01	.....	...	−10	+ 2	− 6	29
52	5	Grehant	0.01	1:7700	22′	−11	−11	0	44.5
52	9	Grehant	0.01	1:7700	23′	− 6	− 6	0	25
54	3	Grehant	0.01	.....	...	− 4	− 4	+ 9	22
54	6	Grehant	0.01	.....	...	− 7	− 5	+ 3	−4.5
41	5	Grehant	0.01	.....	...	− 9	− 8	+ 6	137.8
33	8	Grehant	0.01	.....	...	− 8	− 8	+ 9	0
30	9	Grehant	0.01	.....	...	− 5	− 3	+24	31.25
47	4	Grehant	0.01	.....	...	−14	−15	0	55.5
56	6	Ether	0.01	1:7700	20′	− 2	+ 2	+ 3	71.5
43	5	Grehant	0.0088	.....	...	− 3	− 3	0	33.3
38	3	Grehant	0.0084	.....	...	−11	−11	0	38.4
61	5	Grehant	0.006	.....	...	+ 9	+ 5	0	57
36	1	Grehant	0.0047	.....	...	− 1	+ 1	+14	26.6
51	2	Grehant	0.0042	1:18,287	56′	− 8	− 6	+12	25
61	9	Grehant	0.004	1:19,250	8′	+ 5	+ 2	0	100
51	1	Grehant	0.0021	1:36,000	...	− 6	− 6	+24	44
52	1	Grehant	0.00125	.....	...	0	0	24	0
52	4	Grehant	0.00125	.....	...	0	0	0	11.1
53	3	Grehant	0.00125	.....	...	− 8	− 8	0	0

* Dose, 0.01 cc. per kilogram; for a man weighing 75 Kg., 11¼ grains (0.75 Gm.).

In two dogs there was no response in the first experiment with one eighth of the estimated dose, but dog 53 showed a 16.7 per cent increase of flow when given one eighth of the dose of theobromine sodium acetate, and dog 58 showed a 78 per cent increase when given one sixth of the estimated dosage of theobromine.

In the cases in which no response occurred with more than one eighth of the estimated dosage, there was reason to assume a previous dilatation, as such instances occurred in other than the first injection, except when chloretone anesthesia was used. Because of failure in response or the smaller increase in flow with chloretone anesthesia, even when doses larger than normal were used, it was determined to investigate the effect of chloretone when injected intravenously. This is well shown in table 7. Similar results were obtained in two other experiments. It

TABLE 7.—*Effect of Chloretone*

Experiment*	Drug	Dose per Kg.		Effect: Blood Pressure: Systolic	Effect: Blood Pressure: Diastolic	Effect: Pulse	Per Cent Increase in Flow
1	Theobromine sodium salicylate	0.00125	.....	0	0	0	0
2	Theobromine sodium salicylate	0.00125	.....	0	0	0	50
3	Theobromine sodium acetate	0.01	.....	— 4	— 4	+ 9	22.2
4	80 per cent alcohol	0.3 cc.	.....	— 4	— 4	— 6	0
5	Chloretone in 2 cc. of 80 per cent alcohol	0.027	After 120′	—16	—20	—57	69
			After 180′	—18	—20	—60	77
			After 240′	—12	—14	—60	169
6	Theobromine sodium acetate	0.01	After 5 min.	— 7	— 5	+ 3	—4.15
7	Theobromine sodium salicylate	0.01	After 11 min.	0	+ 2	—12	15.4

* Dog no. 54 (7.4 Kg.).

will be noted in the table that when one eighth of the estimated dose of theobromine sodium salicylate was given, there was no response, but when the same amount was added to that already in the circulation, five minutes later there was a 50 per cent increase in flow. Because chloretone was so much more readily soluble in alcohol, the effect of 0.3 cc. per kilogram of 80 per cent alcohol injected slowly into the circulation was observed. There was a slight decrease in blood pressure and in pulse rate, but no change in the volume of the return flow through the coronary sinus. Chloretone, 0.027 cc. per kilogram, dissolved in 80 per cent alcohol, was then injected into the circulation. This caused a marked decrease in blood pressure and in pulse rate, with a great increase in coronary flow. When a full dose of theobromine sodium acetate was given five minutes later, there was a decrease in the coronary flow, as would be anticipated with a further fall in pressure in the presence of an extreme dilatation. Sixteen minutes after the injection of chloretone,

the volume flow had decreased to a point where a full dose of theobromine sodium acetate was able to elicit a slight response.

A similar check with chloroform (0.0058 cc. per kilogram) in dogs under ether anesthesia showed respectively in three experiments no change in flow, an increase of 3.7 per cent and an increase of 29.4 per cent.

The effect of sodium salicylate and sodium acetate was investigated in order to determine their influence on the action of the corresponding theobromine salts. Sodium acetate in three experiments in doses of 0.01 cc. per kilogram gave no result in one case, and an increase in the coronary flow of 37.5 per cent and 26.6 per cent in the two other cases. Sodium acetate in doses of 0.01 cc. per kilogram in three experiments gave increases of 120, 47 and 83.5 per cent in the coronary flow, and in a dose of 0.0076 cc. per kilogram, an increase in flow of 89 per cent. It is to be observed, however, that the double salts of theobromine in the experiments cited showed no advantage over theobromine when used in corresponding dosage.

The elapsed time between the administration of the drug and the effect on the coronary flow decreased with increased dosage and increased concentration in the blood. With fractional doses, a considerably longer time was necessary before a maximal effect occurred.

SUMMARY

It will be observed that the results recorded in this paper are similar to those obtained in perfusion experiments on the isolated heart, and especially those reported by Heathcote.[9] The order in point of efficacy are: theobromine and its salts, theophylline ethylenediamine, theophylline sodium acetate and caffeine. A vasodilator effect on the coronary arteries, as shown by an increased return flow through the coronary sinus, is shown with doses corresponding to the average human doses, and fractions of such doses.

9. Heathcote, R. St. A.: J. Pharmacol. & Exper. Therap. **16**:327, 1920.

UNDULANT FEVER PRESENTING THE CLINICAL SYNDROME OF INTERMITTENT HYDRARTHROSIS *

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Malta fever is gradually assuming a prominent rôle among the infectious diseases of this country. In 1906, Craig [1] reported the first case of Malta fever contracted in the United States from a natural source and not through laboratory infection. From 1905 to 1924, several reports of similar cases appeared in the American literature (Yount and Looney,[2] Gentry and Ferenbaugh,[3] Lake [4] and others). Although there may be some doubt about the source of infection in the case described by Craig,[1] the infection in the subsequent cases could with considerable certainty be traced to goat's milk.

Although *Bacillus abortus* of Bang had been recognized as a cause of abortion in cattle for many years, and infection by the organism was known to be widespread among cattle in many countries, including the United States, it was not until the work of Shaw [5] and the later investigations of Evans [6] that it became evident that *Bacillus abortus* and *Brucella melitensis* were organisms which are almost indistinguishable by cultural, morphologic and serologic examination. In a continuation of her work, Evans [7] has included under the broad term *Brucella melitensis* strains from human, porcine, caprine and equine sources.

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* Presented in abstract at the meeting of the Association of American Physicians, Washington, D. C., May 3, 1928.

* From the Biological Division of the Medical Clinic of the Johns Hopkins University and Hospital.

1. Craig: The Symptomatology and Diagnosis of Malta Fever, with the Report of Additional Cases, Internat. Clin. **4**:89, 1906.

2. Yount and Looney: Malta Fever, with a Preliminary Report on Cases Occurring in Arizona, Arizona M. J. **1**:18, 1913.

3. Gentry, Ernest R., and Ferenbaugh, Thomas L.: Endemic Malta Fever in Texas, J. A. M. A. **57**:1045 (Sept. 23) 1911.

4. Lake: Malta Fever in Southwestern United States, Pub. Health Rep. **37**: 2895 (Nov. 24) 1922.

5. Shaw: Mediterranean Fever Reports, London, parts 4, 1905-1907, vol. 16.

6. Evans, A. C.: Further Studies on Bacterium Abortus and Related Bacteria, J. Infect. Dis. **22**:576, 1918.

7. Evans, A. C.: Serological Classification of Brucella Melitensis from Human, Bovine, Caprine, Porcine and Equine Sources, Pub. Health Rep. **38**:1948 (Aug. 24) 1923.

The first infection in man proved to be due to *Brucella melitensis*, variety abortus, was reported by Keefer,[8] in 1924. Keefer's study suggested that infection by *Bacillus abortus* might occur in man through the use of milk [9] or milk products obtained from infected cows and under such circumstances might produce in man a disease similar to Malta fever. Since the publication of Keefer's paper, instances of infection by *Bacillus abortus* have been reported from all parts of the country. In the reported cases, emphasis is usually laid on the fact that the goat could be excluded as a source of infection or that the infection was probably derived from cow's milk. During the past year three cases of undulant fever have been observed in the Johns Hopkins Hospital. The diagnosis was confirmed by recovery of *Brucella melitensis* from the blood stream in all three instances.

Hardy [10] has studied the prevalence of the disease in Iowa, basing the diagnosis on positive agglutination tests, and has found it to be probably as common as typhoid fever and paratyphoid fever combined. Abortus infection has recently been reported from Canada (Scozzafave and Warner [11]), and Kristensen [12] has collected 150 cases in Denmark.

Sir David Bruce [13] defined Malta fever as "A disease of long duration characterized clinically by continued fever, profuse perspiration, constipation, frequent relapses, rheumatoid or neuralgic pains, swelling of the joints or orchitis . . ." The pains in the joints are considered characteristic, and in many cases are a distressing feature, necessitating at times a differential diagnosis from acute rheumatic fever. Shaw [14] reported a case in which the patient had swollen, painful joints. In the cases of Gilmour and Kennedy,[15] there was suppuration of the costosternal and costochondral articulations, and *Brucella melitensis* was recovered in pure culture from the pus. One patient of

8. Keefer, C. S.: Report of a Case of Malta Fever Originating in Baltimore, Maryland, Bull. Johns Hopkins Hosp. **35**:6, 1924.

9. More detailed history of Keefer's case brings out the fact that the patient, in the course of his duties as laboratory technician in the department of histology, collected fresh material from hogs at a slaughter house. From the study of the patient's strain Dr. Theobald Smith concluded that the infection was probably of porcine origin.

10. Hardy: Malta Fever, Pub. Health Rep. **43**:503 (March 2) 1928.

11. Scozzafave and Warner: Burcella Abortus Infection in Man, Canad. M. A. J. **19**:177, 1928.

12. Kristensen, M.: Undulant Fever in Denmark, Ugesk. f. Laeger **90**:869, 1928.

13. Bruce: Undulant Fever, in Osler: Modern Medicine, ed. 3, 1920, vol. 1, p. 634.

14. Shaw: Undulant Fever in America, Science **67**:217 (Feb. 24) 1928.

15. Kennedy: Notes on a Case of Chronic Synovitis, or Bursitis, Due to the Organism of Mediterranean Fever, J. Roy. Army M. Corps. **2**:178, 1904.

Watkins and Lake,[16] after apparent recovery from undulant fever, was left with "chronic lumbago."

The excellent clinical descriptions of undulant fever by Keefer,[8] Kristensen,[12] Grigni and Savorini,[17] Kern,[18] Hardy [19] and others portray the disease and its bizarre manifestations in considerable detail, and no attempt will be made in this communication to review this phase of the subject at length. It is desired, however, to direct attention to one manifestation of undulant fever which hitherto has not been described in relation to this disease. Although it is possible that certain instances of intermittent hydrarthrosis may have been, in fact, caused by *Brucella melitensis*, an actual association between the clinical syndrome of intermittent hydrarthrosis and undulant fever has not before been recognized.

REPORT OF CASE

History.—G. J., aged 47, an electrician, living in Virginia, entered the Johns Hopkins Hospital on Nov. 3, 1927, complaining of swelling of the knees.

The family history revealed the fact that his father had died at the age of 74 of heart trouble, and his mother at the age of 70 of cancer of the stomach. No member of his family had ever suffered with diseases of the joints.

The past history showed that he had measles, chickenpox and mumps. Seventeen years ago, at the age of 30, he was ill for six weeks with fever that was termed "typho-malaria," as it was unaffected by quinine. The fever was intermittent in type, with remissions in the morning and rises in temperature as high as 103 F. in the evenings. Anorexia, general arthralgia, malaise, loss of weight and profuse sweating accompanied the fever. While recovery was slow, it was considered complete. Previous to the onset of this illness he was working on a farm in Virginia and had been engaged in slaughtering hogs.

The patient had never married. His habits were exemplary.

Present Illness.—He considered himself in excellent health until the onset of his present illness, which he dated definitely to the last week in March, 1927, when on a cold, wet evening, he stood on a street corner conversing with a friend for an hour or more. On arising the following morning he was aware of a soreness in the tendons behind both knees "as if they had been exercised too much." So far as he knew there had been no undue physical strain. When he walked his knees were stiff, both knees being equally affected. After two days of this discomfort the right knee began to swell and continued to do so for approximately three days, and then the swelling subsided as suddenly as it had risen. For about a day the left knee felt normal, but to his surprise when the swelling in the right knee was at its height, the left knee enlarged also and followed precisely the course taken by the right. During the period of enlargement the knees were stiff, but there was no local redness or heat, and locomotion was not seriously embarrassed.

16. Watkins, N. W., and Lake, G. C.: Malta Fever with Especial Reference to Phoenix, Ariz., Epidemic of 1922, J. A. M. A. **89**:1581 (Nov. 5) 1927.

17. Grigni and Savorini: Clinical and Epidemiologic Symptoms of Undulant Fever, Gior. di clin. med. **9**:359, 1928.

18. Kern, R. A.: Clinical Aspects of Brucella melitensis, Variety Abortus Infection in Man, Am. J. M. Sc. **176**:405, 1928.

19. Hardy, A. D.: The Epidemiology of Undulant (Malta) Fever in Iowa, Pub. Health Rep. **43**:2459 (Sept. 21) 1928.

The patient said that this sequence of events, running in cycles of seven days each, continued with great regularity from the onset of his trouble to the day of admission to the hospital. The only change that he noted was a slow but steady increase in stiffness with consequent difficulty in walking. By August, 1927, he had to give up his work. He entered a local hospital, where a "glassful" of fluid was removed from each knee several times without any effect on the well established periodic swelling.

With the onset of the swellings in the joints the patient began to feel generally run down, though never sufficiently so to go to bed. His appetite was poor, and he experienced an almost constant dull headache. Occasionally he felt chilly and then hot, so that he thought he had fever. There were no sweats. He lost 23 pounds of weight (10.4 Kg.) in six months.

Physical Examination.—Examination of the patient revealed a temperature of 99 F.; pulse rate, 100; respirations, 22; blood pressure 120 systolic and 75 diastolic; height, 166.3 cm.; weight, 117 pounds (53.1 Kg.).

The mucous membranes were pale, and there was a slight, yellowish pallor of the skin. He had evidently lost weight. The gait was abnormal, obviously due to inability to flex properly the right knee. There were no cutaneous hemorrhages or hemorrhages in the ocular fundi. The tonsils were not enlarged, but there was moderate reddening of the right anterior tonsillar pillar. Several enlarged glands were felt in the anterior and posterior triangles on both sides of the neck. The epitrochlear glands were not felt. The thyroid gland was not enlarged. The lungs were clear to percussion and auscultation. The heart was not enlarged, and the sounds were loud and clear. No thickening of the radial or brachial arteries was noted. The liver and spleen were not felt, nor did they seem enlarged to percussion. The prostate gland was small and firm.

Examination of the muscles showed them to be of good tone and bulk. There were no disturbances in the recognition of all sensory stimuli. All the tendon reflexes were equal and active on the two sides.

The skeletal system was normal with the exception of the right knee joint. It was much larger than the left. There was no redness, discoloration, increased temperature or edema of the overlying skin. Definite ballottement of the right patellar was demonstrated together with a considerable accumulation of fluid in the quadriceps pouches and obliteration of the normal bony markings of the knee joint. There was definite crepitation when the joint was moved, and passive flexion beyond 90 degrees caused considerable pain. The left knee presented no apparent abnormality.

Laboratory Examination.—The blood count showed red blood cells, 4,070,000; hemoglobin, 83 per cent; white blood cells, 9,440; polymorphonuclear neutrophils, 71 per cent; polymorphonuclear eosinophils, 1 per cent; lymphocytes, 22 per cent; mononuclears, 6 per cent. Examination of the smear revealed no abnormality. The urine on admission had a specific gravity of 1.025; no sugar; albumin, 1 plus. Microscopic examination of the urine showed a rare hyaline cast and many white blood cells and epithelial cells. After several days on a high fluid intake the urine became normal and remained so throughout the patient's sojourn in the hospital.

The Wassermann reaction was negative. Phenolsulphonphthalein excretion was 60 per cent in two hours. The tuberculin test (0.1 mg.) intracutaneously was negative. The basal metabolic rate was +6. No hypersensitivity to epidermal extracts, dairy products, grains, fish, vegetables or fruits was found by intracutaneous tests. X-ray pictures of the knees revealed a slight degree of infectious arthritis (fig. 1). The other larger joints were normal on roentgen examination.

Figures 2 and 3 show the appearance of the knees at a time when the swelling was maximal in one and minimal in the other.

Fig. 1.—Roentgenogram of the knees showing a slight degree of infectious arthritis.

Fig. 2.—Appearance of the knees at a time when the swelling was maximal in one and minimal in the other.

Fig. 3.—Appearance of the knees at a time when the swelling was maximal in one and minimal in the other.

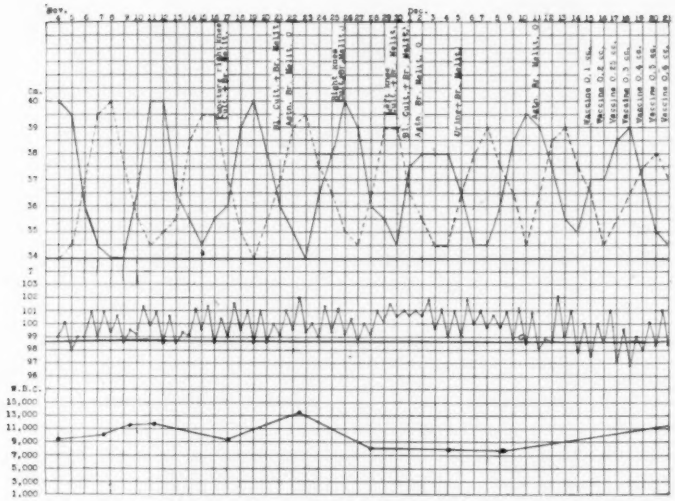

Fig. 4.—The curves represent the fluctuations in the size of the knee joints, variations in temperature and the white cell count. The patient weighed 117 pounds (53.1 Kg.). The red blood cells numbered 4,000,000; the hemoglobin content was 83 per cent; the polymorphonuclear neutrophils, 71 per cent; the eosinophils, 1 per cent, and the mononuclears, 28 per cent.

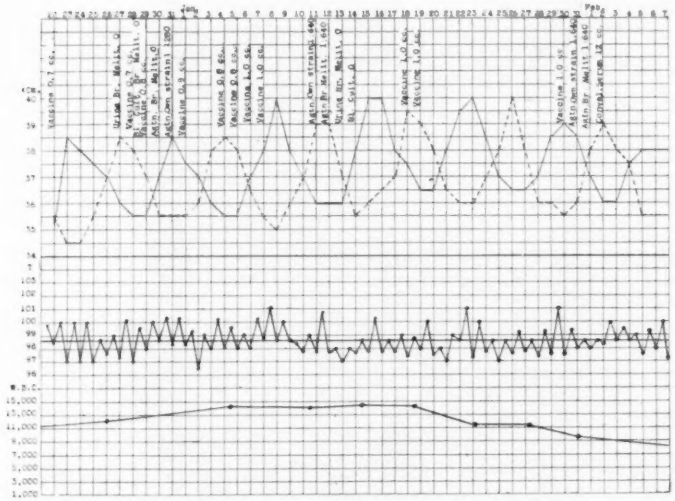

Fig. 5.—The curves represent the fluctuations in the size of the knee joints, variations in the temperature and the white cell count. The patient weighed 124 pounds (56.2 Kg.). The red blood cells numbered 4,000,000.

Course of Illness.—Both knee joints were measured daily at the same hour, and reference to figures 4 and 5 confirms the patient's story of an extraordinary regularity in the swelling. It can be seen from the charts that for weeks without interruption, between Saturday evening and Sunday evening, the swelling in the right knee reached a maximum. The left knee followed a similar schedule, approximately three and a half days after the right.

In the charts the highest and lowest temperatures for the day and the leukocyte counts are plotted. The occurrence of persistent fever associated with slight leukocytosis suggested a search for some infection.

Accordingly on November 17, the right knee was punctured, and 30 cc. of a thick, brownish yellow fluid, clotting quickly, was withdrawn. The white blood cells of the fluid numbered 5,200 per cubic centimeter; 75 per cent were lymphocytes, and 25 per cent polymorphonuclear leukocytes. A small quantity of a similar fluid was again withdrawn from the right knee on November 26, and from the left knee on November 30.

Direct smears from these fluids stained by the method of Gram, contained a moderate number of tiny gram-negative bacilli frequently occurring in pairs. The fluid was cultured on the occasion of each tapping. On November 22, and again on November 30, cultures were made from the blood stream. On November 5, 5 cc. of urine was injected into the groin of a guinea-pig. From each assay an organism was recovered which proved on further study to belong to the *Brucella melitensis* group.

On November 22, the patient's serum failed to agglutinate organisms of hygienic laboratory strains of *Brucella melitensis* 426, 428 and 456. Again on November 30, there was no agglutination, using these strains as well as the organisms recovered from the patient's own knee joints. A third attempt to demonstrate agglutinins in the patient's serum on December 11 failed.

Treatment.—A solution of potassium arsenite, sodium cacodylate and quinine in appropriate doses had no effect on the fever, swelling of the knees or the patient's symptoms. Because of the fact that it was impossible to demonstrate agglutinins in the patient's serum for *Brucella melitensis*, administration of an autogenous vaccine was begun on December 15. He received 13 cc. of vaccine between Dec. 15, 1927, and Jan. 30, 1928, prepared from organisms recovered from his knee joints and blood stream.

On February 2, he was given intramuscularly 12 cc. of serum from a patient (A. S. reported by Keefer) who had recovered from Malta fever and whose serum contained agglutinins for the patient's organism. On February 11 an additional 8 cc. was given, and this dose was repeated on February 19.

Further Course.—Prior to the administration of vaccine the clinical picture had not changed; the patient had not gained weight; the fever had persisted, and the knees had continued to swell as they had done on admission. Thirteen days after administration of the vaccine was started, the patient's serum, in a dilution of 1:640, agglutinated the organisms recovered from his knees and blood stream; fourteen days later his serum, in a dilution of 1:640, agglutinated known strains of *Brucella melitensis*. Almost immediately after commencement of the use of the vaccine, the temperature began to approach normal. His appetite improved, and he felt generally stronger. He felt that the stiffness in his knees accompanying the peaks of swelling was less noticeable. Reference to figure 6 will show the effect on the hydrarthrosis.

Following the administration of convalescent serum, the improvement was striking. The temperature became normal and remained so. He felt well and gained weight rapidly. The leukocytosis disappeared; the hemoglobin percentage

rose to 90, and the red blood count to 5,000,000. Two blood cultures made on Dec. 28, 1927, and on Jan. 14, 1928, remained sterile for twenty days, and cultures from the urine were negative for *Brucella melitensis*. The stiffness and pain largely disappeared from the knees, and while the base line of measurement of the joints became elevated, the fluctuations in the size of the joints diminished greatly. He was discharged on Feb. 24, 1928.

Unfortunately he was forced to return immediately to work, which necessitated standing for from six to eight hours daily. The knees began to swell again, but caused him little, if any, discomfort.

The patient was last heard from on Sept. 15, 1928. He had been constantly at work since leaving the hospital, but the periodic swelling of his knees had slowly returned. For two days each week the pain and stiffness were marked, but the

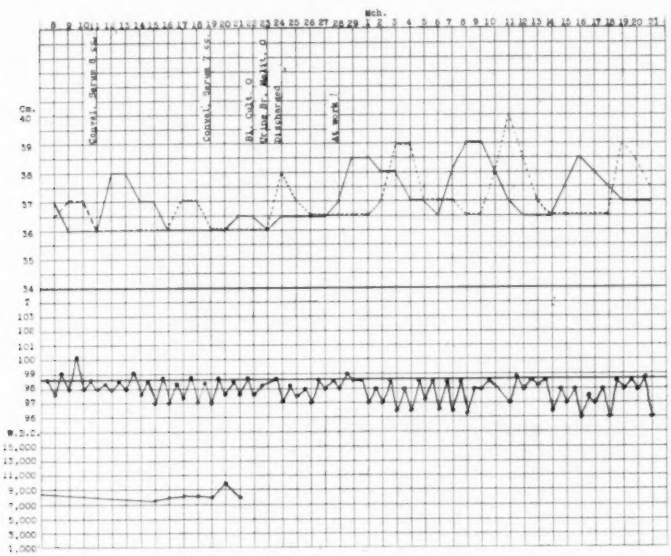

Fig. 6.—The curves represent the fluctuations in the size of the knee joints, variation in the temperature and the white cell count. The patient weighed 131 pounds (59.4 Kg.). The red blood cells numbered 5,000,000; the hemoglobin content was 90 per cent; the polymorphonuclear neutrophils, 57 per cent; the eosinophils and basophils, 5 per cent, and the mononuclears, 38 per cent.

remainder of the week he passed in moderate comfort. Otherwise, he had remained well; none of the symptoms associated with his general infection had returned and estimations of the temperature in the morning and evening, daily since discharge, showed that he had remained afebrile.

BACTERIOLOGIC OBSERVATIONS

Cultures from Joint Fluids.—Approximately 1 cc. of fluid was allowed to flow freely over the surface of slants of beef infusion agar of p_H 7.4 at the bedside immediately after aspiration. The tubes were

incubated at 37.5 C., and no culture was pronounced sterile until it had been incubated for twenty days. The first signs of growth occurred on the sixth, seventh and eighth days, in cultures made on three separate occasions.

Blood Cultures.—Two methods were used. In the first, 8 cc. of blood was laked with 80 cc. of sterile distilled water and centrifugated at high speed for fifteen minutes. The supernatant fluid was discarded, and the sediment mixed with 45 cc. of dextrose agar of p_H 7.4 and 8 cc. of sterile ascitic fluid and poured into several Noguchi tubes. These were stoppered with cotton swabs and allowed to incubate at 37.5 C. for twenty days before being discarded.

Results of Agglutination Tests Made with Normal Serum, the Patient's Serum and the Patient's Organisms Against the Patient's Serum, Brucella Melitensis and the Serum of One Known to Have Malta Fever

	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:2560	1:5120
Normal serum vs. patient's organisms	No agglutination									
Normal serum vs. known Brucella melitensis	No agglutination									
Patient's serum vs. patient's organisms										
11/30/27	0	0	0	0	0	0	0	0	0	0
12/11/27	0	0	0	0	0	0	0	0	0	0
12/28/27	0	0	0	0	+	+	+	0	0	0
1/11/28	0	0	0	0	+	+	+	0	0	0
1/30/28	0	0	0	+	+	+	+	0	0	0
2/ 2/28	0	0	0	+	+	+	+	0	0	0
Patient's serum vs. known Brucella melitensis										
11/22/27	0	0	0	0	0	0	0	0	0	0
12/11/27	0	0	0	0	0	0	0	0	0	0
12/28/27	0	0	0	0	0	0	0	0	0	0
1/11/28	0	0	0	+	+	+	+	0	0	0
1/30/28	0	0	0	+	+	+	+	0	0	0
2/ 2/28	0	0	0	+	+	+	+	0	0	0
Patient's organism vs. serum from a patient known to have Malta fever	0	0	0	+	+	+	+	0	0	0

Controls of suspensions of the organisms in each test were negative.

The second method consisted of inoculating each of five flasks containing 80 cc. of beef infusion broth p_H 7.4 with 2 cc. of the patient's blood and incubating for twenty days before pronouncing them sterile. The organism was recovered by the use of both methods.

Identification.—The organism grew luxuriantly on beef infusion agar. Grayish, opaque, moist, rounded colonies, from 2 to 5 mm. in diameter, first appeared on the sixth day after inoculation. The organisms were nonmotile and did not retain Gram's stain. Both bacillary and coccoid forms occurred in the cultures, but the bacillary forms predominated in young cultures. Organisms frequently occurred in pairs, but longer chains were seldom seen. There was no fermentation in maltose, levulose, mannite, saccharose, raffinose or dulcite.

Agglutination Reactions.—Macroscopic agglutination tests of the patient's serum in dilutions from 1:10 to 1:5120 at 56 C. for two hours were made with organisms from fluid from the patient's knee joints and from the blood, as well as with three organisms of the *Brucella melitensis* group obtained from the hygienic laboratory.[20] Normal human serum and saline controls were set up in each test. The results are given in the accompanying table.

The proagglutinoid zones were present in all tests. Cooling the serums for forty-eight hours in the icebox, heating them undiluted for an hour at 56 C., or allowing them to stand undiluted at room temperature for several weeks had no effect on the appearance of the proagglutinoid zone. Allowing the racks of tubes to stand at room temperature for seventy-two hours after they had been read caused a disappearance of the proagglutinoid zone. No explanation is given for this observation.

Animal Inoculation.—The patient's strain was sent to Dr. Theobald Smith for study. The lesion produced by inoculation into guinea-pigs simulated closely, but not absolutely identically, that produced by bovine *Bacillus abortus*.

COMMENT

There is no doubt that this patient had undulant fever. The recovery of *Brucella melitensis* from the blood stream, the presence of agglutinins in the serum of high titer, together with the clinical course, make the diagnosis undeniable.

Joint symptoms commonly form part of the picture of undulant fever, and occasionally are pronounced. In this case the joint symptoms were singularly striking. The effusions into both knee joints appeared and disappeared with clocklike regularity every seven days, and this remarkable course of events continued for months without interruption. When the patient was first seen, a diagnosis of intermittent hydrarthrosis was made. In an effort to determine the etiologic factor of this obscure malady, it was discovered that the patient had Malta fever and that *Brucella melitensis* existed in large numbers in the synovial effusions.

Hydrops intermittens articulorum has been known and regarded as one of the curiosities of medicine since 1845. Perrin [21] first described the condition and cited as accompaniments of the hydrarthrosis slight fever, aching joints, headache and anorexia, all of which were present in the clinical picture of the case reported here.

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20. These strains were sent by Dr. Alice C. Evans.

21. Perrin: Cas curieux de contracture partielle intermittente, Union méd. **25**: 821, 1878.

In 1864, Moore [22] reported the second case and three years later added another.[23] Eighty-three instances of the disorder are now to be found in the literature. The one feature common to all cases is the periodic hydrarthrosis, the time intervals separating attacks varying from several days to several weeks.

Garrod [24] and Benda [25] have written excellent descriptions of the disorder. Diagnosis rarely offers any difficulty, for intelligent patients can prophesy with great accuracy not only the day but often the hour at which an attack will commence. Age, sex and social status apparently have no bearing on the patients who present this rare picture. Blanc [26] reported an instance in which mother and daughter were victims of intermittent hydrarthrosis. In the great majority of cases the condition involves one or both knee joints, which were believed to have been perfectly healthy previous to the onset of hydrarthrosis. In certain instances, patients give a history of antecedent arthritis or trauma.

There has been no uniformity of opinion regarding the etiology of this peculiar disease. Senator [27] reported two cases and concluded from a review of the literature that the etiology was not the same in all cases: in some instances the periodic effusions depending on abnormalities in the vasomotor system, and in others on inflammatory changes in the affected joints.

Because of the frequent preceding history of ague (Perrin,[21] Moore,[22] Marsh [28] and others), the view was long held that malarial fever might be responsible for the periodicity of intermittent hydrarthrosis. The discovery by Ross of the short and constant life cycles of the malarial parasites necessitated the abandonment of this conception. Many, but not all cases, are associated with high fever; in others, an enlarged spleen has been observed. In Bierring's [29] case, the patient

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22. Moore: Periodical Inflammation of Knee Joint, Lancet **1**:485, 1864.

23. Moore: Two Cases of Periodical Inflammation of the Right Knee Joint, Tr. Medico-Chir. Soc. Edinburgh **1**:21, 1867.

24. Garrod: Concerning Intermittent Hydrarthrosis, Quart. J. Med. **3**:207, 1909-1910.

25. Benda: Intermittirende Gelenkwassersucht, Allg. med. Centr.-Ztg. **69**:471, 483, 495, 507 and 521, 1900.

26. Blanc: Observation d'hydrarthrose intermittente héréditaire, Loire méd. **17**:287, 1898.

27. Senator: Ueber intermittirende Gelenkwassersucht, Charité-Ann. **21**:224, 1896.

28. Marsh: An Affection of the Knee Possibly Due to Malaria, Tr. Clin. Soc. London **38**:147, 1905.

29. Bierring, W. L.: Intermittent Hydrarthrosis, J. A. M. A. **77**:785 (Sept. 3) 1921.

noted a regularity of the swelling of his knee joint following an illness described as typhoid fever.

There have been a number of efforts to demonstrate organisms in the fluid aspirated from affected joints. In all attempts, heretofore, so far as one is aware, the fluids have shown no growth on culture. Hartmann,[30] in the joint fluid from a typical case, observed a "typhoid-like bacillus" but was unable to cultivate it. Pulawski [31] noted a *"Diplococcus"* in direct smears from the synovial fluid but could not identify it.

These facts suggest the possibility that other cases presenting the clinical syndrome of intermittent hydrarthrosis might prove, on careful bacteriologic examination, to be instances of infection by a member of the *Bacillus abortus* group. It might be argued that in the majority of the reported cases of hydrops intermittens articulorum there are no signs or symptoms of a chronic infection. This is likewise true at present, of the patient in the case reported, for whereas he has regularly recurring effusions into the knee joints he is afebrile and asymptomatic, and it is further well recognized that mild symptoms of undulant fever frequently pass unheeded by the patient.

It is hoped that this report will stimulate careful bacteriologic study of cases of intermittent hydrarthrosis and systematic observations of the joints in cases of Malta fever.

SUMMARY

1. A case of infection by *Bacillus abortus* arising in Virginia is reported.

2. In addition to many of the features of undulant fever the patient presented a periodic swelling of the knee joints, diagnosed intermittent hydrarthrosis.

3. Organisms of the *Brucella melitensis* group were isolated repeatedly from the blood stream and from fluid from the knee joints.

4. Specific agglutinins appeared in the blood after the administration of an autogenous vaccine.

5. Definite disappearance of the signs and symptoms of the infectious disease followed the administration of *Brucella melitensis* vaccine and serum from a patient who had recovered from undulant fever.

6. There was amelioration of the subjective joint disturbances and a temporary alteration in the hydrarthrosis following this treatment.

30. Hartmann: Ueber einen Fall von Spondylitis deformans mit intermittierendem Hydrops der Gelenke, Inaug. Diss., Konigsberg, 1889.

31. Pulawski: Ein Fall von periodischer Gelenksschwellung, Wien. klin. Wchnschr. **27**:421, 1914.

7. It is concluded that in this case the intermittent hydrarthrosis was part of the general picture of infection from *Brucella melitensis*, and it is suggested that infection by a member of this group of organisms might prove to be the cause of the clinical syndrome, intermittent hydrarthrosis, in other patients.

8. It should be emphasized that during the period in which *Brucella melitensis* was cultured from the blood and urine, there were no agglutinins in the patient's serum. Thus differential diagnosis cannot be based solely on agglutination reactions.

THE PATHOLOGIC ASPECT OF SOME EPILEPSIES*

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The literature contains numerous examples of material lesions in the cerebrum which are associated with typical epileptic convulsions of the jacksonian or general type. Among the latest pathologic records may be mentioned: tumors of the pontocerebellar angle, the angular gyrus, the temporal convolutions and the pituitary gland; dilatation of the lateral ventricles; hemorrhage in the occipital lobe, and thrombophlebitis of the under surface of the frontal lobe.[1] It is evident that a pathologic process in many portions of the brain may be accompanied by epileptic seizures, and these areas may therefore be considered as epileptogenous zones. In the present contribution a pathologic lesion in a rather rare localization of the brain is described; the lesion, during the patient's life, was a stimulating surface for convulsive discharges. In the absence of clinical evidences of gross pathologic involvement of the brain, particularly in cases of focal epilepsy, it is well to refer to the possibilities of invasion of the ventricles and especially of the lateral ventricles.

Ventricular walls are covered by ependymal lining membranes consisting of columnar and ciliated epithelium. In the ventricular cavity in a state of suspension lie the choroid plexuses with their villi, which are constantly brought into contact with the ependyma of the ventricular walls. Should the latter be in a state of inflammation or otherwise abnormally disturbed, there would be sufficient cause for the villous processes of the choroid plexuses to produce an irritation in the brain and, through the process of diffusion of the stimulus to the cortex along association or commissural fibers, to lead to reactions such as epileptic convulsions. Two examples are presented incriminating the ventricular cavities of the brain as the direct cause of epileptic convulsions during the patient's illness. In one, the ventricular ependyma alone was found to be diseased; in the other, the choroid plexuses were chiefly affected. No other lesion was found in either of the brains. As I am concerned in this paper chiefly with the pathologic aspect of the problem, the details of the clinical pictures of the cases will be omitted.

The patient in the first case was a middle-aged colored man, who presented frequent convulsive attacks (with loss of consciousness) confined to the left arm, with turning of the head to the left side. There were also ataxia, involvement of the deep sensibilities in the left

* Submitted for publication, Jan. 26, 1929.

1. Gordon, A.: J. Nerv. & Ment. Dis. **61**:142, 1925.

arm, and finally left-sided hemianopia. A right-sided lesion was suspected in the brain. A decompressive operation was declined by the patient's relatives. The patient died during one of these attacks.

At autopsy all the abdominal and thoracic viscera were found to be normal. After being hardened, the brain presented on transverse anteroposterior section most uncommon observations, which were confined exclusively to the anterior cornua of the lateral ventricles. The lesion was pronounced in the right horn, and only slightly evident in the left horn. There was an unusually large quantity of fluid in both cornua. The ependyma had lost its uniform smoothness and was covered by numberless miliary nodules. Histologically, the latter presented cells of partly necrotic material; some of them were under the ependyma; some had destroyed it and some were in its surface. Their relative size was not equal, some of them being larger and longer than others; some were close to the surface and formed thick branches at a certain distance from the surface. They consisted of crowded round cells which followed the branches of the original nodules. Many vessels in this vicinity had mononuclear cells similar to those of the nodules. Some blood vessels were thrombotic and greatly dilated, and had thickened walls. In the latter, the inner layer was shriveled and torn in some places. The ependyma itself immediately beneath the miliary nodules was much thickened and covered thickly between the nodules by round cells. In some areas there was solution of continuity of the ependyma, which solution continued deep in the subependymal tissue. The inner walls of the separated portion were covered with round cells. As to the nature of the ependymal nodules, it is difficult to say. They did not have the histologic composition of tubercles. It would seem reasonable to call them miliary gummas. This view is substantiated, I think, by the fact that many vessels in the vicinity had mononuclear cells in their walls.

In the second case the patient was a boy, aged 10, who had had epileptic seizures since the age of 5. They were all of a generalized character and typical in their individual manifestations. There were no somatic symptoms deserving special mention.[2] The patient died from an intercurrent bronchopneumonia.

At autopsy all thoracic and abdominal viscera were found to be intact. A systematic study of the brain was made both macroscopically and microscopically. Special emphasis was laid on the histologic state of the cortex, in addition to a detailed examination of all tracts, fibers and nuclei. The only pathologic tissue that could be determined was found in the choroid plexuses, and in the ependyma of the anterior horn of the lateral ventricles. Externally, the plexuses appeared to be

2. Gordon, A.: J. Nerv. & Ment. Dis. **67**:445, 1928.

greatly congested, and were thick, large, and hard under the fingers. The histologic study of the sections was made after the usual process of hardening. The staining was done with ammonia-carmine. The numerous glomeruli, which are held together by the delicate connective tissue stroma and which present a villous-like appearance, were seen with their cubic epithelial cells and their main constituents, namely blood vessels. The latter were filled with thrombi of all sizes, and some of them were surrounded by a thickened external wall as the result of an inflammatory process evidently of long standing (fig. 1).

Fig. 1.—Choroid plexus. The blood vessels are filled with thrombi and surrounded by thickened external walls.

One finds in this instance, therefore, an original inflammation of the choroid plexus followed by hemorrhages within them. Since the choroid plexuses are practically a convoluted mass of highly vascular processes of the pia which covers the walls of the ventricles, sections of the latter were examined microscopically. They were found to be thickened and similar to the plexuses. Their blood vessels were also filled with thrombi but not to the same extent (fig. 2). The entire pathologic process was therefore continuous from one to the other, with this difference, however, that the hemorrhage was less pronounced in

the membrane of the ventricular walls than in the plexuses. The disorder consequently lies in the pia mater of the lateral ventricles. The other ventricles of the brain were normal in appearance and on histologic studies.

COMMENT

To sum up, in the two cases described in this paper the pathologic process is confined to the lateral ventricles of the brain and to their contents, thus demonstrating that in addition to the other organic

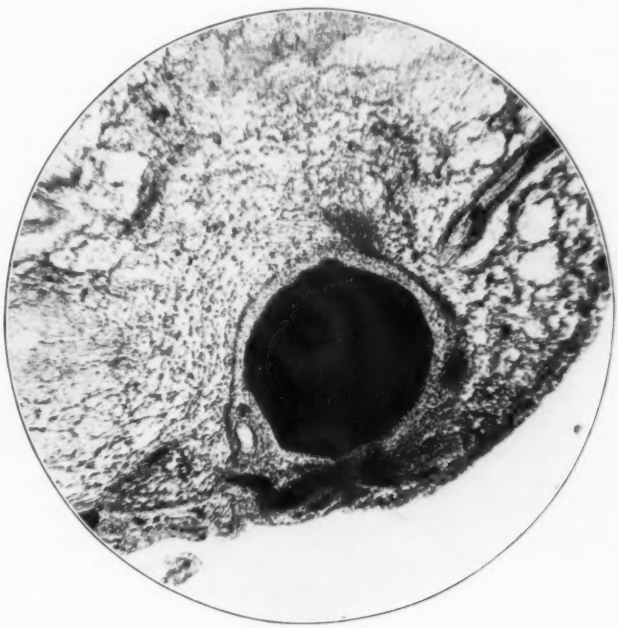

Fig. 2.—Choroid plexus. The pia of the walls of the ventricles is thickened. The blood vessels are filled with thrombi.

localizations of epilepsy in the cerebrum the ventricular cavities may play the same rôle of an epileptogenous zone. Ferrier, in his "Functions of the Brain," referred to his experimental investigations on the ventricular walls, which on electrical stimulation produced spasmodic muscular contractions. Ferrier's observations had been corroborated by experiments of Corville and Duret.

The pathologic observations of the two cases are not a common occurrence. Ventricular foci have been rarely reported in connection with epilepsy. Not only the lining of the ventricular walls of the

choroid plexuses, but a pathologic state of the physical properties of the cerebrospinal fluid in the ventricles may play an important part in cerebral irritation resulting in convulsive seizures. In a recent contribution [3] a case of hydrocephalus was described in which frequent epileptic attacks were caused by increased tension of that fluid in the lateral ventricles. A withdrawal of a certain amount of that fluid from the lateral ventricles was followed by freedom from seizures during nine months.

The particular interest of the present contribution lies in the observations on the patient in the second case who during life presented manifestations of the common form of so-called idiopathic epilepsy in which an underlying organic lesion is ordinarily not expected. Besides the interesting histologic observations, the cases are instructive from the standpoint of localizations. Apparently, functional disorders may have an organic basis in areas other than those which are classically established. The present contribution adds a new rare document to those already existing which concern a vast variety of pathologic foci found in organic epilepsy. It warrants being placed on record on account of the unusual localization and the peculiar character of the lesions. It might also have been of interest to consider the mechanism of epileptic convulsions in cases of involvement of the ventricular walls and of the ependyma with the choroid plexuses. One might also have been interested in considering the association, commissural and projection pathways extending from the stimulated or irritated surface to the motor cells of the cortex, which, in the last analysis, are the province of the discharge of motor power resulting in convulsive seizures. Finally, it might have been of interest to be reminded of the experimental work done in that direction. But the object of the present contribution is not to show the physiologic or the clinical aspect of the problem of so-called functional or organic cases of epilepsy, but to present exclusively a pathologic document of an uncommon involvement of the contents of cerebral ventricles to the exclusion of any other lesion in the brain.

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3. Gordon, A.: Hydrocephalus with Cessation of Persistent Epileptic Convulsion after Puncture of the Lateral Ventricles, J. A. M. A. **88**:1234 (April 16) 1927.

MOTILITY OF THE RECTUM IN NORMAL AND IN CONSTIPATED SUBJECTS*

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Operative experiments on laboratory animals and roentgen studies on man have yielded most of the knowledge concerning the muscular activity of the colon. The information obtained with the roentgen rays is limited because only gross changes are revealed. Operative experiments on animals also have some shortcomings due to inability to elicit subjective symptoms or to the abnormal conditions which anesthesia and surgical intervention represent.

This is a study of the movements of the rectum before and after a meal and further shows the symptoms produced by the prolonged presence of a mass in the rectum. A balloon inserted into the lower colon of man through a proctoscope and filled with water has served as a medium for recording movements of the colon. Although the lower bowl was emptied of fecal matter before the experiment started, the results are interpreted as applying to a filled colon because the size and shape of the balloon are not unlike a formed fecal mass.

METHODS

Twenty-one medical students who had healthy bowel action and twelve patients from the clinic who were constipated and users of cathartics were the subjects. All experiments were started shortly after the subject had defecated normally or as the result of an enema. All records were made while the subject was lying on his right side. A toy balloon measuring about 12 by 2.5 cm., tightly fastened to rubber tubing, was well greased with petrolatum and inserted into the lower sigmoid and rectum through a proctoscope. Long tissue forceps were used to hold the balloon in place while the proctoscope was being withdrawn; 150 cc. of water warmed to 38 C. was forced into the balloon. The pressure was measured with a mercury manometer (in about half of the experiments). Then the tubing from the balloon was connected with a water manometer placed on a shelf about 5 feet (1.5 meters) above the level of the subject. Tracings were made on a slowly moving drum for periods of at least thirty minutes before and after the subject ate. Sixteen subjects carried the balloon all day (from six to twelve hours) and were instructed to note especially the occurrence of symptoms such as headache, malaise or mental haziness.

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RESULTS

The intracolonic pressure in millimeters of mercury was measured in ten normal and four constipated subjects. As shown in the tables, the pressure varied from 11 to 21 mm. The average was between 17 and 20 mm. (Ten of the fourteen readings were in this range). There

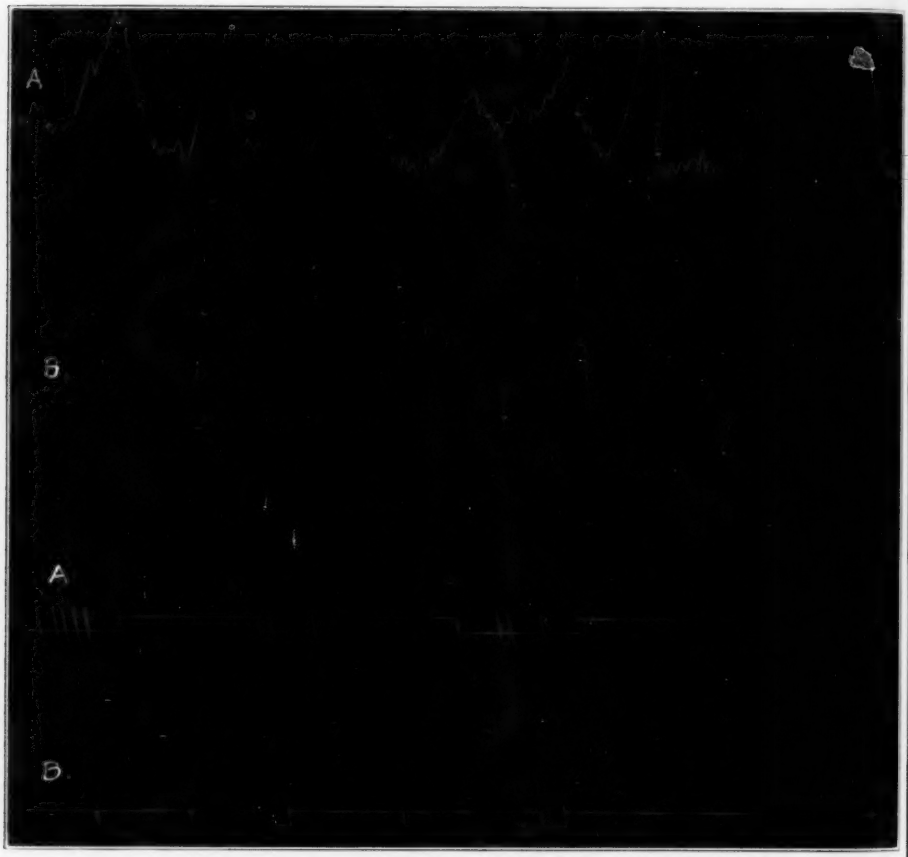

Fig. 1 (subject C. R.).—Steep contractions which occurred before and after eating in normal subject. *A* indicates before a meal and *B*, after a meal.

was no appreciable difference in the pressure of the two groups (constipated and normal).

The sensation produced after the balloon was filled with water varied as to degree, but in all there was an immediate sensation of fulness accompanied by a desire to defecate. Usually, after a few

Fig. 2 (subject E. W.).—Tonus rhythm which occurs before and after eating in constipated subject. No steep contractions occurred. *A* indicates before a meal and *B*, after a meal.

Fig. 3.—Record of normal subject showing only tonus rhythm before a meal.

minutes, the sensation lessened or disappeared. However, in all of the normal group painful "urges" developed. These painful sensations lasted only a few seconds and generally became more frequent and severe as time went on. The most painful sensations were experienced by the sixteen who carried the balloon all day. The pain of one was so severe that he was unable to retain the balloon more than two hours. A signal magnet was used to record painful sensations while tracings were being made.

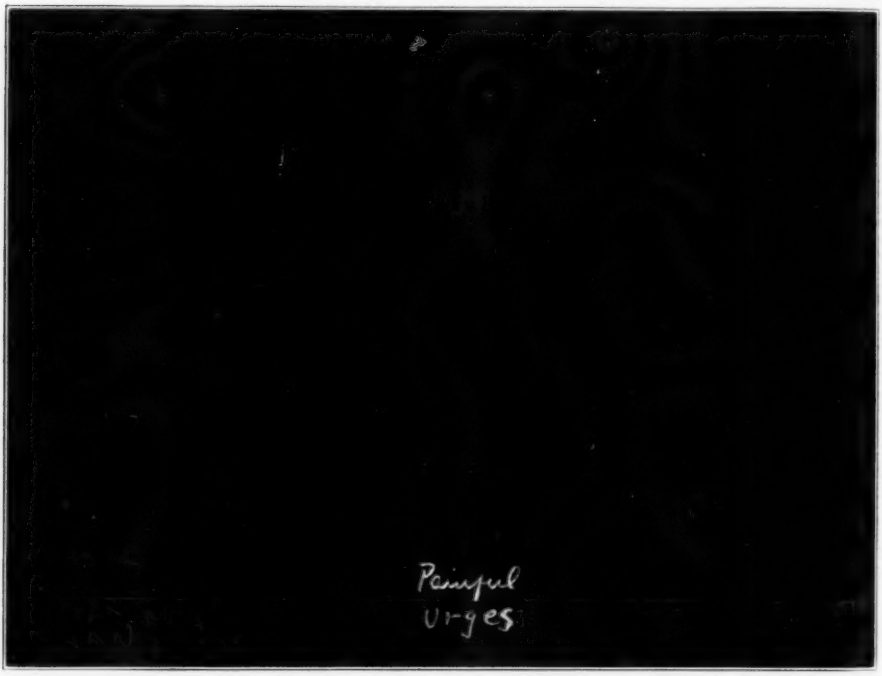

Fig. 4.—Record of same subject shown in figure 3, showing steep contractions after eating.

After the balloon had been in place several hours, all subjects complained of a tight sensation in the hamstring group of muscles which some described as an ache. One complained of pain along the course of the left sciatic nerve. After the removal of the balloon, many had the sensation of "walking on air."

No symptom characteristic of the autointoxication syndrome was produced, even in those who carried the balloon for long periods.

The tracings show two types of contractions: slow, slight, rhythmic elevations (a tonus rhythm) and steep contractions. A tonus rhythm was present in all of the normal group and in ten out of twelve of the constipated group. The steep contractions were present in all of the normal group but in only four of the constipated group. In five, steep contractions occurred only after meals. The painful urge was

TABLE 1.—*Summary of Tracings in Group with Normal Bowel Action*

Subject	Painful Urge	Tonus Rhythm	Steep Contractions	Painful Urge	Tonus Rhythm	Steep Contractions	Pressure in Mm. of Hg
T. V.	Slight	+	0	Moderate	+	++	..
F. A.	0	+	0	0	+	+ ?	..
M. E.	0	+	0	Marked	+	++	..
L. E.	Moderate	+	++	Marked	+	++	..
G. U.	Marked	+	++++	Marked	+	++++	..
C. R.	Marked	+	++++	Marked	+	++++	..
B. V.	0	+	+	0	+	+	..
W. A.	Slight	+	++	Slight	+	+++	16
S. I.	0	+	+++	0	+	++	..
B. El.	0	+	+	Moderate	+	+	17
S. A.	No determination			Moderate	+	+++	..
C. H.	No determination			Marked	+	+ ?	18
P. O.	Slight	+	+++	Slight	+	+++	22
H. O.	0	+	+	Marked	+	++++	17
H. E.	Marked	+	+++	Moderate	+	++	21
L. A.	Marked	+	++++	Marked	+	+++	18
A. D.	Marked	+	++++	Marked	+	++++	18
C. R.	Slight	+	++	Marked	+	+++	..
C. A.	0	+	++	Slight	+	++	15
C. An.	Slight	+	0	Moderate	+	+	19
B. Ehr.	0	+	++	Slight	+	++	18

TABLE 2.—*Summary of Tracings in Group Who Were Constipated*

Subject	Painful Urge	Tonus Rhythm	Steep Contractions	Painful Urge	Tonus Rhythm	Steep Contractions	Pressure in Mm. of Hg
E. W.	0	+	0	0	+	0	..
J. N.	0	+	0	0	+	0	..
J. D.	0	+	0	0	+	+	..
J. N.	0	+	..	0	+	+	..
C. G.	0	+	0	0	+	0	..
C. F.	0	+	0	0	+	0	..
N. S.	Slight	+	..	Slight	+	+	..
C. P.	0	+	0	0	+	+?	..
M. B.	0	0	0	0	0	0	18
E. M.	0	0	0	0	0	0	18
V. C.	0	+	0	0	+	0	11
K. H.	0	+	0	0	+	0	12

always associated with a steep contraction wave and was usually synchronous with it. Many of the steeper waves, however, were not accompanied by painful sensations.

COMMENT

Welch and Plant [1] have recently studied the activity of the colon in dogs by inserting balloons filled with water into the colon through permanent fistulas. They have demonstrated irregularly recurring

1. Welch, P. B., and Plant, O. H.: A Graphic Study of the Muscular Activity of the Colon, Am. J. M. Sc. **172**:261 (Aug.) 1926.

changes of tonus usually with superimposed contractions and in three experiments on human beings have shown similar activity in the lower colon. They demonstrated increased muscular activity after eating when the colon was full and refer to this as a feeding reflex. Our experiments on a larger series of human beings have confirmed the presence of two types of activity in the normal colon, and this is interpreted as applying to a filled colon because the balloon is the equivalent of a fecal mass.

Comparative studies on constipated and normal subjects have shown that steep contractions and a synchronous painful urge are infrequent in the constipated group. This seems to indicate that the threshold for sensation in the constipated man is raised. It also seems likely that the steep contraction is one of the involuntary aids to the act of defecation and occurs infrequently in those who are constipated.

In five experiments, the steep contraction did not occur until food had been taken. This might be taken as evidence of a gastrocolic reflex. In the constipated group neither painful urges nor increased activity was demonstrated after eating.

Alvarez [2] expressed the belief that the symptoms of so-called autointoxication, such as headache, malaise, dopiness and mental haziness which commonly are present in constipated people, are due to the mechanical distention of the lower colon by the fecal mass. He produced such symptoms by stuffing the rectum with cotton. Our studies do not support his contention.

SUMMARY

Tonus rhythm and steep contractions are normal movements of the filled lower colon of man.

A balloon shaped like a fecal mass in the lower colon of man produces symptoms described as a painful urge but does not produce symptoms like those ascribed to autointoxication.

Painful urges are synchronous with steep contractions. In some experiments there is increased activity after eating (gastro-colic reflex).

Patients who are constipated and have the habit of taking cathartics do not complain of painful sensations while the balloon is in the colon and have infrequent steep contractions.

2. Alvarez, W. C.: Intestinal Autointoxication, Physiol, Rev. **4**:352, 1924.

Book Reviews

THE CLIMACTERIC (THE CRITICAL AGE). By GREGORIO MARANON, Professor of Medical Pathology in the Madrid General Hospital, Member of the Royal National Academy of Medicine. Translated by K. S. Stevens. Edited by Carey Culbertson, M.D. Price, $6.50. Pp. 425, including index and 18 illustrations. St. Louis: C. V. Mosby Company, 1929.

The first five chapters deal with the alleged pluriglandular factors in the menopause symptoms: the ovarian factors, the thyroid factors, the hypophysial factors and the suprarenal factors. There is a chapter on the vegetative nervous system during the menopause. There are eleven chapters describing the symptoms in relation to the menopause, and in addition three chapters dealing with the psychic symptoms. In these chapters the author touches on nearly every variety of disease that may occur during the menopause. There is one chapter on the climacteric of the male and two chapters on the therapy of climacteric symptoms in the female.

Dr. Maranon is a facile and prolific writer in the field of the endocrines. Unfortunately, he is not a critical one. He tells one in the preface that "all the theory in the book is based on the present knowledge of the internal secretions much of which does not go beyond mere hypotheses. Yet we have profited by them in our work." This profiting by endocrine hypotheses appears in accepting practically all of them as proved facts, and on that basis building up a hypothetic diagnosis and therapy. Almost any disease known to man may, of course, appear as an incident during the period of the menopause. Because of the frequency of nervousness and neurocirculatory disturbances in the menopause, Maranon concludes that there is a condition of hyperthyroidism and hypersuprarenalemia nearly always present. In fact, one is told categorically that "independent of the size of the thyroid gland castration creates, if not actually active hyperthyroidism, at least a hyperthyroid predisposition." Part of the menopause symptoms are said to be due to an excess secretion of epinephrine. In addition, the author puts great emphasis on "constitution or temperament" in the etiology of the disorders of the climacteric. The ease with which the author obtains evidence for his views may be indicated by a few examples:

"Let us consider the differences between the inhabitants of northern and southern Spain. Those of the northern are of vigorous athletic type; they are frequently fair, blue-eyed and of even temperament. On the contrary, the inhabitants of southern Spain are thin and swarthy. Their eyes are dark and their teeth magnificent. They are restless and superficial. Nothing can better explain the contrast between these two groups than their different thyroid constitutions." One is further told that "during the critical involution period the other endocrine glands react anatomically and functionally thus compensating the insufficiency of the failing ovary. This reaction is determined by temperament." "If a woman exhibits signs of a hypersuprarenal temperament, in the menopausal crisis those phenomena which we have given as probably dependent on hypersuprarenalism will predominate. This temperament is, like the hyperthyroid, very frequent."

Maranon (p. 103) lists among other factors which influence the chronologic climacteric "the color of the hair." One is further told that "very dark women are almost always hyperthyroid, hyperpituitary and hyperovarian." Evidence for this statement is cited from a novelist, Bécquer. In fact, illustrative material is cited almost as frequently from novels as from the medical and scientific literature or the author's own practice. For example, the case of Sarah, the wife of Abraham, is referred to as "the oldest known case of post-climacteric conception." In connection with the hair (p. 127) "sexual impulse causes curled hair, in both men and women, especially in certain mentalities of elemental sexuality and little

delicacy." While criticizing the freudian school in certain aspects, the author at times seems to outdo even the freudians. For example, one is told "man's social status has a sex value. His business and professional success is a means of sexual attraction."

In the chapters dealing with the general etiology of menopause symptoms, the author is hypothetic and verbose. The actual descriptions of the symptoms are diffuse and contains too much duplication, but the poor quality of the book is probably best indicated in the chapters on the treatment of climacteric symptoms. He recommends ovarian therapy by mouth, and states that "the results of ovarian therapy in the climacteric are excellent in general." As treatment for the alleged hyperthyroidism of menopause he recommends the defunct "antithyroid serum." The reviewer wonders where the author and the American editor have been the last twenty years. As general therapy for menstrual disturbances of the climacteric, the author recommends the following regimen: "1. Subject the patient to rest and institute general care of the uterine hemorrhages. 2. Administer the usual classic remedies proper in these cases such as ergot, hydrastis, hamamesis, etc. 3. Add, as a regulator of the ovarian function a discrete dose of ovarian extract." Such procedures will give no information on the influence of ovarian extracts.

"The ovarian extracts, total or partial, have a positive hypotensive effect. The existence of hypertension is therefore an indication for intensifying ovarian therapy." In cases of cardiac insufficiency during the climacteric he recommends the use of "whole ovarian extracts in vigorous doses." In asthenia of the climacteric one is told that "ovarian treatment is of indubitable usefulness." Pruritus is said to "respond perfectly to ovarian opotherapy." Obesity during the climacteric also "yields well to ovarian opotherapy." And finally, in the paragraph on the therapy of masculine climacteric, the author says that he has "employed ovarian extracts in men with good results."

Contrast this endocrine euphoria of Dr. Maranon with sober clinical conclusions of Dr. Novak (Glandular Therapy, American Medical Association, 1925): "rational as ovarian therapy appears to be in some conditions, the results are rarely striking and often nil, to the level-headed observer. It cannot be assumed that a commercial extract can replace the normal ovarian secretion in the patient's body, or, for that matter, that it originally contains any of the active hormones of the ovary. Here lies the crux of the whole problem, whose solution will depend in large measure on the work of the biochemist. Until this day, the physician who uses ovarian therapy should keep his feet on the ground and not let himself be carried away by the exaggerated claims of those who have something to sell, or the ill advised and premature reports of honest but deluded professional colleagues who have not yet learned the dangers lurking in the 'post hoc propter hoc' method of reasoning."

This monograph of Maranon advances neither medical science nor medical practice. It is amusing and easy reading if the busy practitioner is willing to wade through reams of verbosity and waste much time in hunting down the old and established facts in a jungle of fiction.

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